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REVIEW ARTICLE

Dynamic Propagation and Impact of Pandemic Influenza A (2009 H1N1) in Children: A Detailed Review

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Abstract

Influenza is a highly contagious respiratory infection caused by the circulating Swine flu virus. According to the World Health Organization (WHO), the unique blending strain of influenza A H1N1 2009 (Swine Flu) is a pandemic affecting several geographical regions, including India. Previous literature indicates that children are "drivers" of influenza pandemics. At present, satisfactory data were not available to accurately estimate the role of children in the spread of influenza (in particular 2009 pandemic influenza). However, the role of children in the spread of pandemics influenza is unclear. Several studies in children have indicated that the immunization program decreased the occurrence of influenza, emphasizing the significance of communities impacted by global immunization programs. This article provides a brief overview on how children are a key contributor to pandemic Influenza A (2009 H1N1) and we would like to draw your attention to the need for a new vaccine for children to improve disease prevention and a positive impact on the community.

Abbreviations

ALRI	Acute lower respiratory infections
WHO	World Health Organizations
HA	Hemagglutinin
NA	Neuraminidase
ARDS	Acute Respiratory Distress Syndrome
ILI	Influenza-like illness
POCT	Point of care testing
RIDT	Rapid influenza diagnostic tests
LAIV	Attenuated influenza vaccines
IIV	Inactivated influenza vaccine
ACIP	Advisory Committee on Immunization Practices
DCGI	Drug Controller General of India
AAP	American Academy of Pediatrics
IAV	Influenza A virus
IBV	Influenza B virus

Introduction

Influenza virus (commonly known as 'flu virus' or 'swine flu virus') is a life-threatening pathogenic circulating virus, preferably infecting the respiratory tract. It has a unique ability to cause a recurrence epidemic and pandemics in individuals of all ages. In growing children, it causes acute lower respiratory infections such as bronchitis and pneumonia [1]. The proportion of hospitalizations for children can reflect the severity of the disease. It is estimated that 10% of all hospitalizations in children below 18 years of age are due to respiratory diseases and cause 3% of post-neonatal deaths worldwide [2]. The transmission of influenza contributed to several factors, including the probability of infection, the susceptibility of the population and the risk of contact between highly prone and infected individuals. Swine flu virus is transmitted from person to person mainly through respiratory air droplets caused by the sneezing or coughing of infected persons [3]. Pandemic influenza A (2009 H1N1) is a viral disease that appears with influenza-like symptoms in children and young adults compared to the other adult population.

Unlike other respiratory infections, especially seasonal or recurrent influenza, the clinical severity and pathogenicity recorded with 2009 H1N1 was slightly milder; still, it is mysterious. A remarkable gene arrangement combining the genetic material from avian, human and swine flu viruses have been observed for this pandemic infection [4].

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It was assumed that swine are a logical candidate and work as a "mixing vessel" for the novel genetic shift of avian, swine, and human viruses, since they share a common signaling receptor (epitopes) that classifies both strains equally. Thus, swine play a significant role in the occurrence of swine flu viruses as well as in the initiation of human pandemic outbreaks [5].

The first outbreak of H1N1 infection in 2009 originated in California, North America, but was reported in the Mexican village on 18 March 2009 [6]. Subsequently, the extent of the outbreak covered around 10–20% of the global population and finally switching the human seasonal flu virus (H1N1) [7]. By 11 June 2009, the World Health Organization (WHO) declared it to be the first global pandemic of the twenty-first century and confirmed post-pandemic phases in August 2010. As per the WHO guideline, the 2009 H1N1 virus is currently considered to be a seasonal Swine flu virus [8]. The highest number of hospitalizations was seen among children under the age of five [9].

On the other hand, many empathies depend on studies available in the public domain. All studies have a different sample size, reflecting the accurate estimate of the population attribute; however, they have been over-or underestimated in different age groups. A 2009 study of H1N1 showed that the incidence rate of contact with children is very important for the transmission of the virus in children [10]. Therefore, Pediatric vaccination has been universally implemented with global acceptance as an effective solution to reduce the mortality rate and prevent the spread of 2009 H1N1 [11].

Data from global surveillance and notification systems show a higher risk of H1N1 infection in children under two years of age, individuals with underlying medical/clinical conditions and morbidly obese people. Further, low serum level of IgG2 was also associated with the severity of the 2009 H1N1 infection, primarily in pregnant women [12].

The purpose of this review is to provide an overview of the burden of influenza in children worldwide, with a special focus on the 2009 H1N1 novel strain. The review will also highlight the role of children in the 2009 H1N1 spread (Fig. 1).

Epidemic Status

Epidemiological studies have shown that the extent of infection with the pathogenic swine flu virus varies from year to year in different geographical regions of the worldwide. Extensive ecological differences are known to influence the prevalence of infection in various populations with varying degrees of severity. Genetic predisposition and lifestyle-mediated risk of infection may also affect the outcome of an epidemic. Available data demand extensive studies covering a diverse areas and age groups at different time periods to recognize the level of H1N1 infection in the community and their spread among various groups of individuals. The novel viral strain of the twenty-first century was first documented in Mexico in April 2009; the virus has spread rapidly to a number of countries around the globe, including India, which has affected more than 214 countries and caused 18,449 deaths in the epidemic [13].

According to a study, about 60% of patients were under 18 years of age, indicating that young adults were prone to H1N1 infection as compared to older adults. A total of 1,82,166 clinically established cases of H1N1 and 1,800 deaths are reported by WHO [13]. The 2009 H1N1 is less deadly than the other 20th-century outbreaks such as the Spanish flu (H1N1) in 1918, the Asian flu (H2N2) in China in 1957, and the Hong Kong flu (H3N2) in 1968 [14]. It is believed that the Spanish flu was the most serious influenza pandemic and the result of influenza A, which affected about 50% of the world population and caused about 50 million deaths [15].

In India, 7 million deaths have been reported across different social classes, genders and geographical locations [16]. Up to January 2011, about 46,142 laboratory-confirmed cases and more than 2728 deaths from various parts of the country have been reported in India [17]. The highest incidence of H1N1 2009 was reported in Maharashtra, Madhya Pradesh, Telangana, Karnataka, Jammu & Kashmir, Rajasthan, Gujarat, Delhi, and Tamil Nadu [18]. The first Indian report of 2009 H1N1 was recorded in June 2009 from Hyderabad City of Telangana State and the first mortality from Pune. Only 937 deaths and 9972 proven cases of pandemic influenza A were reported in Maharashtra [19].

Growing children and young adults were most susceptible to infection and every 2 out of 5 infected children were under 14 years of age. Mortality (27,236 cases) and morbidity (981 deaths) are higher due to the 2009 H1N1 pandemic in India [20]. At the beginning of 2015, H1N1 2009 re-emerged in India, and more than 2000 deaths from 35,000 recorded cases were reported in mid-February 2015 [19]. Seasonal patterns of influenza in tropical and subtropical countries vary from year to year which is consistent with connectivity, herd immunity, community practices, moisture, indoor swarming, and heat at a particular latitude. High rates of cases have been observed for during the rainy season worldwide. In India, the highest rate of influenza movement was detected during the rainy season [21]. The burden of pandemic influenza in global populations is summarized in Table 1.

Biochemistry and Mechanism of Infection

Influenza A is a negative-sense ssRNA virus with a spherical or filamentous shape belonging to the orthomyxoviridae family. In addition to the point mutation in this virus, the

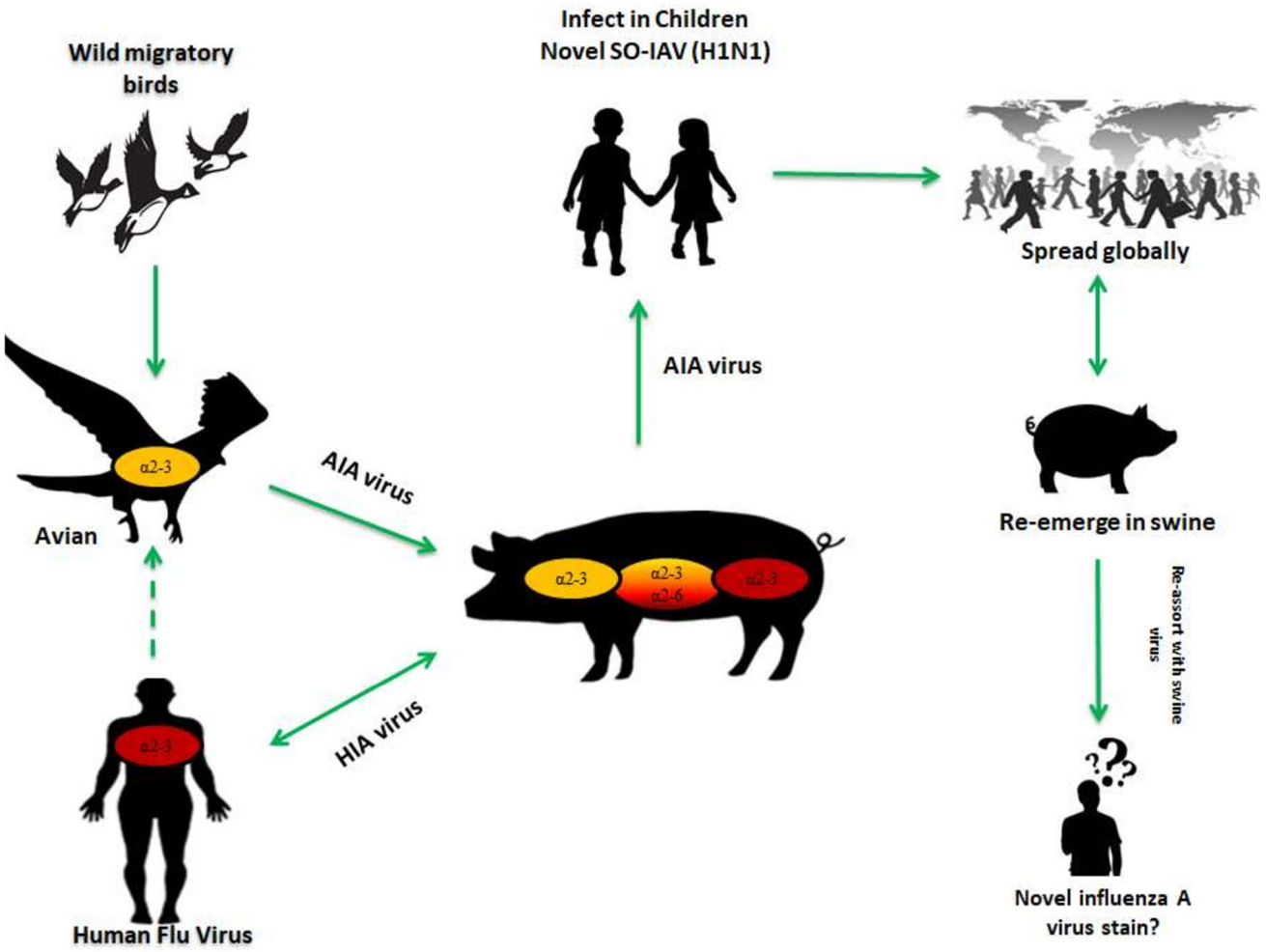

Fig. 1 The swine is a potential source for reassortment and mixing of influenza A viruses. The antigenic and genetic similarities between avian, human and swine influenza A viruses (IAV) make swine more susceptible to infected by both avian and human influenza strains. IAV from swine can also infect human. Avian and human Swine flu virus glycoprotein (HA) is preferentially binds to α-2, 3 and α-2, 6 SA receptors, which are independently expressed on the cells of respiratory track, whereas swine can express both types of SA receptors proving that swine act as a "mixing vessel" for avian and human influenza A viruses and that reassortant virus combination is responsible for the origin of novel pandemic influenza A (2009 H1N1) virus which effect in children age group. Children are highly susceptible to seasonal as well as influenza A infection and play key role in spreading "human to human" influenza infection. Re-entry of human IAV H1N1 to swine may give rise to a novel future influenza A strain which may further leads to pandemic/epidemic. Solid lines: Represent confirmed infection events, Dotted line: Depicted occasional infection event

genetic reassortment of RNA segments confers a unique ability to alter the host genome and the virulence factor. Swine flu viruses can be categorized on the basis of genetic/antigenic variations of glycoproteins on their surface, namely hemagglutinin (HA) and neuraminidase (NA). Both HA and NA play a significant role in the pathogenesis of viral disease and act as a significant target for vaccine design. Swine flu virus is multifaceted and involves the spread of different viruses among different animal classes.

Wild duck and shorebirds serve as the usual reservoirs of Swine flu virus. Birds infected with viruses containing combinations of 18 HA (H1-H18) and 11 NA (N1-N11) subtypes. Several aquatic birds act as primary natural reservoirs for low pathogenicity avian Swine flu viruses. In 2014, two novel lines of influenza A virus H17N10 and H18N11 subtypes were detected in rectal swabs of the small yellow-shouldered bat and the flat-faced fruit-eating bat [46]. To date, only glycoprotein's subtypes N1, N2 and H1, H2, H3 are known to have positively adapted to humans [47].

Human respiratory cells and avian host cells differently express α-2, 3, and α-2, 6 sialic acid receptors, respectively, Swine can express both α-2, 3 as well as α-2, 6 sialic acid receptors. Due to the segmented viral genome, when two different types of Swine flu viruses infect the same host it can be interchanged, that generates a novel fusion called 'reassortant'. Such 'reassortant' is a key factor and potential

Table 1 Pandemic influenza burden in global populations

Reference	Country	Season	No. of patients	No. of hospitalization Confirmed	No. of fatal cases	Age group (year)	No. or % of cases
[22]	England	2009 (Jul–Nov)	9630	NR	138 Cumulative incidence /1 lakh	< 1 1–4 5–14	1000 1100 3100
					Fatality/1 lakh	< 1 1–4 5–14	30 27 11
[23]	Germany	2009 (Apr–Aug)	9950	3630	NR	up to 2 15–19	6 90
[24]	Netherland	2009 (Apr–Jun)	115	51	0	0–4 5–9 10–14 15–19	4% 22% 16% 12%
[25]	Australia (Queensland)	2009 (Apr–Jun)	593	16	0	0–4 5–9 10–14 15–19	21.6% 16.8% 28.7% 27.6%
[26]	US	2009 (Apr–Jul)	1557	205	NR Fatality	0–4 5–14 0–4 5–14	113 147 25 11
[27]	France	2009 (Apr–Jun)	4867 all patients	358 confirmed	NR	0–9 10–19	26 35
[28]	New Zealand	2009 (Apr–Aug)	3179	972	16 Cumulative Incidence /1 lakh	< 1	219
					Fatality/1 lakh	< 1	150
[29]	Australia	2009 (Apr–Jul)	223	NR	NR	0–4 15–19	3% 37%
[30]	Australia	2009 (May–Aug)	5106	1214 hospitalization, all ages	1	0–4 5–9 10–14 15–19	306 116 90 108
[31]	US	2009 ending	NR	725	NR	< 5 5—17	325 500
[32]	Ireland	2009 (Apr–Oct)	NR	205	4	0–4 5–9 10–14 15–19	9.7% 6.1% 4.7% 10.2%
[33]	US	2009 (May–Jun)	NR	272	19	0–2 2–4 5–9 10–17	8% 7% 11% 18%
[34]	Japan	2009 (Apr–Dec)	NR	10,487	85	0–4 5–9 10–14 15–19	11 8 4 1
[35]	US	2009 (Apr–Aug)	NA	NR	36	0–4 5–17	7 29
[36]	Cyprus	2009 (Jun–Aug)	45	5	0	< 1 1–5	4 10
[37]	Australia	2009 (May–Sep)	NR	977	24	0–18	3
[38]	US	2009 (Apr–Aug)	NR	259	132 Incidence	0–4 5–17	2.45% 0.61%
					Fatality	0–4 5–17	0.026% 0.010%

Table 1 (continued)

Reference	Country	Season	No. of patients	No. of hospitalization Confirmed	No. of fatal cases	Age group (year)	No. or % of cases
[39]	France	2009 (Jul–Nov)	NA	514	Incidence /1 lakh	< 1	2.03
					37 fatality	< 1	3
						1–14	2
[40]	Canada	2009 (May–Aug)	324	235	2	< 3 months	15
						3–5 months	9
						6–23 months	49
						2–5 yrs	66
						6–12 yrs	63
						13–15 yrs	33
[41]	Netherland	2009 (Jun–Dec)	NA	2181 hospitalizations (non-ICU), all ages	53	0–4	565
					Incidence/1 lakh	5–14	350
					Fatality	0–4	5
						5–14	9
[42]	New Zealand	2009 (May–Oct)	3254	1008	Cumulative incidence /1 lakh	< 1	223
						1–4	97
						5–9	84
						10–14	92
						15–19	127
					Fatality 19/1 lakh	5–9	17
						10–14	19
						15–19	23
[43]	UK	2009 (Apr–Sep)	NR	631	29	< 1	42
						1–4	49
						5–15	125
					Fatality	0–15	3.5%
[44]	Canada	2009 (Apr–Jun)	3152	140	7	< 1	48
						1–11	863
						12–18	880
[45]	England	2009–2010 (Apr–Mar)	NA	440	336	< 1	4

source of 2009 influenza pandemic strains [48]. Swine can serve as host for avian and mammalian adapted strains, and thus conventionally assumed to act as a 'mixing vessel' between them, and facilitating the generation of more precarious and pathogenic novel 'reassortant' Swine flu viruses [49].

Influenza A virus has a segmented genome with capsulated matrix 1 (M1) protein, surrounded by host -derived phospholipid bilayer, which interacts with surface glycoproteins (HA and NA) and viral ribonucleoprotein (vRNP) complexes. The ion channel protein matrix 2 (M2), embedded in the virus envelope membrane which is important for the transport of ions across the viral membrane and budding of new cell surface viruses [50].

As an antigen interaction and a fusion initiator, HA has a number of significant functions in the virus infection cycle. HA mediates the direct binding of the virus to specific terminal sialic acid (SA) on the cell surface and regulates the incorporation of viral genetic material through the membrane fusion process. In contrast, NA protein plays a vital role later in infection by eliminating SA from sialyloligosaccharides, which is essential for releasing newly formed virons from the viral envelope and inhibiting the self-gathering of the virus genome [51].

Children Play a Crucial Role in Propagating Pandemic Influenza

It has been observed that children are highly susceptible to both seasonal and pandemic influenza. Children of early age have a maximum hospitalization rate and are the primary route of community infection [52, 53]. In terms of severity and burden of disease, the 2009 H1N1 had a significant impact on the pediatric population [54]. Statistics from three influenza pandemics (Hong Kong flu, Asian flu and Spanish flu) reported the highest rates of disease in school-going children, which was also the main source of infection spread among adults [55].

Several other factors also contribute to the vulnerability of children to infection. Children regularly spend time in crowded places, such as schools, playground and after-school

care, which increases their risk of influenza infection. Such behavioral observation among children contributes disproportionately to the spread of influenza infection and to the amplification of the pandemic. As a result, children are more often and responsible for secondary transmission than adults within their homes.

Many studies have shown the leading role of children in influenza epidemics and pandemics (2009 A/H1N1, 2010–2011 A/H3N2, 2010–2011 A/H1N1, 2012–2013 A/H3N2 and 2013–2014 A/H1N1) with the highest relative risk ratio (RR) among all age groups [56]. Wardell et al. found that the risk of transmission of an infected first child to another child was 21.9%, [95% CI 14.5–30.2] higher than the corresponding risk to live with an adult, 11.4%, RR 1.9, 95 per cent CI 1.2–2.8. Compared to children [6.9%, 95% CI 4.4–10.1], adults were less likely to contribute to the spread of infection by another adult [0.6, 95% CI 0.3–0.96] [57].

The decreased frequency of influenza transmission was also reported during school closure periods compared to open-time schools, indicating the crucial role of school children in the spread of influenza [58]. The contributing role of school-going children decreased significantly during the post-pandemic period, which is likely due to the immunity gained during the pandemic. Furthermore, it has been reported that school-aged children (5–17 years of age) have the highest rates of influenza attack during the 2009 H1N1 pandemic [59]. In the US, during annual epidemics between 1977–1978 and 1980–1981, children aged 0–19 years had a higher risk of infection with influenza A compared to adults with influenza A. compared to adults of any age. In addition, influenza B epidemics in the 1976–1977 and 1979–1980 age groups of 5–14 years show the highest risk of infection [60].

Clinical Manifestation and Hospitalization

Flu causes infection and disease in all age groups of both genders, but children show the highest rates of infection, in particular 40% higher hospitalizations during epidemics [61–63]. Pandemic influenza A infection in children, typical influenza-like symptoms (ILS) such as cough, sore throat, runny nose, headache, fever, muscle aches, and malaise may vary in severity from mild to severe. Some studies have also reported symptoms of vomiting and diarrhea that are more frequent in children than in other age groups [64]. Pneumonia is the most common complication of pandemic influenza A infection. Forty-five cases of 2009 H1N1 in children aged 40 days to 15 years in the Cyprus region; 5 of them were hospitalized (average time of 3.4 days); no influenza-related deaths and typical clinical symptoms were the same [36]. 79 positive cases of pandemic influenza A, with an average age of 5.7 years have been reported to be hospitalized in Birmingham, UK [65].

In Switzerland, 326 PCR confirmed 2009 H1N1 patients were reported, of which 189 (57.97%) patients were less than 5 years age and 38.65% of patients had one or more pre-existing clinical condition. Fever was the most common indication of infection; febrile seizures were most recurrent condition in children of less than 5 years of age. However, bacterial infection observed only in 4% of patients [66].

A serum-based diagnostic study from the USA has shown that most people are likely to be susceptible to 2009 H1N1 infection, but older people have a certain level of cross-protection against pandemic influenza compared to children in this region [67]. The incidence of 2009 H1N1 infection in school-going children was reported to be more prevalent in worldwide, ranging from 34 to 43%. Although the results were inconsistent, the Hong Kong study found higher rates of infection in older children, while another study reported higher rates in younger children [68].

An Iranian study reported that about 50–60% of children with 0–19 years age had more than 40 titers after pandemic [69]. A study showed that the rate of admission in infant over 6 months of age is similar to that in high-risk adults, but an increased admission rate was found in children more than two years of age [70]. One study from India reported that 85 children were positive for 2009 H1N1 virus infection; maximum were boys; about 64.7% were between 5 and 16 year of age. The average age for children was 7.5 ± 3.5 years. The mean period of hospitalization was 5.4 days for the children with a reporting of 3 deaths with Acute Respiratory Distress Syndrome [71].

A study reported in the Pune region of Maharashtra, the highest incidence of influenza-associated hospitalizations and deaths among individuals under 35 years of age at the peak of the flu pandemic. Another study conducted in 2007–2010 around Delhi showed that the percentage of influenza A pandemic infection was higher in age groups between 5 and 18 years of age [72]. Influenza infection causes a socio-economic burden due to the loss of school time for children and working time for their family members [73].

Diagnosis

With the current pandemic influenza A infection and the potential lack of antiviral drugs, especially in developing countries such as India, it is essential for physicians and clinicians to diagnose influenza A cases quickly and precisely. Upper respiratory specimens, including a nasopharyngeal aspirate, a nasal swab plus a throat swab or a nasal wash are collected for H1N1 pandemic testing, preferably after 5 days of onset of illness. Rapid diagnostic testing aids in clinical decision-making, reduces improper use of antibiotics and decreases the visit time of the emergency department [74].

Techniques and methods used to diagnose and detect seasonal influenza A and B include rapid antigen tests, immunofluorescence antibody tests, viral culture, and RT-PCR. Case definition of infection in a person with influenza-like illness (ILI) confirmed by laboratory diagnosis via RT-PCR and/or viral culture of novel circulating influenza A. The high sensitivity and specificity of RT-PCR makes it a gold standard molecular technique for the diagnosis of pandemic influenza.[75].

Point of care testing can be performed quickly in less than 15 min, which provides a significant time advantage over other laboratory-intensive influenza testing methods. The use of rapid influenza diagnostic tests (RIDTs) may also detect influenza A infection quickly, but Centers for Disease Control and Prevention (CDC) is concerned about the use of RIDT due to their lower sensitivity (ranging from 40 to 69%) compared to real-time RT-PCR analyzes [76]. The target population for diagnosis should include individuals who require hospitalization or are at high risk for serious illness. Using the case definition for ILI as a guide to who needs to be tested. However, some groups may have typical clinical presentations, especially infants and children with compromised immune systems requiring influenza A testing.

Antiviral Drugs and Its Clinical Complication

Antiviral drugs are the main strategies for the effective prevention and control of transmission of influenza. Due to the reassortment of genetic alterations in viral oncoprotein, the virus is more resistant to existing antiviral drugs. It is therefore very important to develop novel, potent, targeted therapeutic drugs to overcome the severity and duration of the disease caused by the pandemic virus. Antiviral drugs are most effective when administered within 24 h of onset of disease [77].

Two different classes of antiviral drugs such as M2 ion channel protein inhibitors (rimantadine and amantadine) and NA inhibitors (oseltamivir and zanamivir) are currently approved for use against both influenza A and B virus infections. In addition, NA inhibitor drugs inhibit the release of new viral particles from affected cells and mitigate cell-to-cell infection, while amantadine and rimantadine block the transport of H + ions through the viral M2 protein channel that is essential for their entry into the target cell. Traditionally, both drug groups are very effective in managing and preventing seasonal influenza A. Among these, amantadine is recommended for adults only [78].

Oseltamivir (Tamiflu) is the most commonly prescribed oral drug used in seasonal influenza and swine flu infections, which is highly effective for decreasing otitis media incidence in children aged between 1–3 years, when treatment is started within 12 h of onset of symptoms [79]. Some side effects of drugs have also been reported from various studies. A cross-sectional study in the United Kingdom reported that 18% of children with oseltamivir treated with influenza A had mild neuropsychiatric side effects and one or more subsequent symptoms such as not being able to concentrate precisely, insomnia, feeling confused nightmares and acting strangely [80]. Another study reported frequent vomiting in oseltamivir-treated children as compared to placebo [81].

U.S. FDA approved zanamivir for use as a dry powder in children aged 5–7 years and old age individuals for management as well as prophylaxis of influenza type A or B virus. According to 74 observational studies this drug is beneficial for the reduction of mortality and influenza-related complications [82]. However, its use is limited to individuals with chronic pulmonary diseases such as asthma. Subsequently, two other classes of NA inhibitor drugs were identified for the management of influenza A and B infections [83]. On the other hand, their use is limited to a few countries, including Japan, China, South Korea and the USA [84, 85].

Vaccination

Vaccination is a very effective strategy for preventing and controlling influenza infection, particularly in the high-risk population. Infants and children are highly susceptible to infectious diseases and their complications, including pneumonia, due to their frequent activity in crowded settings. Various groups around the globe are looking to vaccines as a potential defense against a novel strain of pandemic influenza A.

Biochemical changes occurring in the Swine flu virus warrant novel immunizations on an annual basis [86]. Generally, two main types of vaccines have been approved to control influenza infection, namely live attenuated influenza vaccines (LAIVs) and inactivated influenza vaccines (IIVs)/trivalent inactivated vaccines (TIVs) that are US-FDA-accredited for use in children 2 years of age and pregnant women ≥ 50 years of age. LAIV is administered as a nasal spray, whereas TIV is administered intramuscularly via injection and protects against both influenza A/H1N1 and A/H3N2 strains as well as influenza B viruses [87]. In addition, LAIV provides more effective protection than IIV for infants and children. The Advisory Committee on Immunization Practices (ACIP, CDC), preferably recommends LAIV for children aged 2–8 years when available immediately [88, 89]. Recently approved quadrivalent influenza vaccines (QIVs4) [LAIV FluMist ® and three IIV FluarixTM, FluLavalTM and Fluzone ®] followed in 2012–2013 for people between 2 and 49 years of age, which licensed for Influenza B Yamagata and Victoria lineages but are not allowed to be transported and distributed in India [87].

Currently available TIV vaccines are not approved for children under 6 months of age because they may not have a fully mature immune system [88]. Trivalent vaccines, specifically in use, are antigenically homologous to a novel influenza strain. Therefore, this does not require a separate pandemic influenza vaccine. The importance of LAIV marketing and use exists in terms of faster production, a good safety profile, less resource-intensive and cost-effective compared to the inactivated influenza vaccine. In India, after seeing evidence of immunogenicity, quality control and safety in the clinical investigation, pandemic influenza A vaccines have been licensed by the Drug Controller General India (DCGI) and have been available since September 2010 [90]. In the preliminary phase, the Government of India offered > 2.5 million doses of pandemic influenza to immunize high-risk groups, social and medical staff and emergency unit personnel across India, of whom Karnataka alone used ~ 1 million doses [91].

Current epidemiological data indicate that children and younger adults have been deeply infected with the 2009 pandemic influenza A [92]. Therefore, children should be the primary target group for vaccination. According to the American Academy of Pediatrics, the vaccine must be included in the repetitive immunization regimen for children aged 5 to 18 years [93]. The study showed that LAIV was 82% effective against pandemic influenza A in children 2–8 years of age and that its efficacy decreased by 11% in children 9–17 years of age [94].

Recently, the WHO and CDC updated information related to influenza vaccines for the public domain on 28 February 2020 and recommended that all regular dose flu shots be quadrivalent and trivalent for influenza vaccines, including Egg-based Vaccines and Cell-based Recombinant Vaccines for the North of 2020–2021 (https://www.who.int/influenza/vaccines/virus/recommendations/2020-21_north/en/) and southern hemisphere influenza season (https://www.who.int/influenza/vaccines/virus/candidates_reagents/2020south/en/).

The vaccine should be made available to the following people at high risk of becoming infected with H1N1 swine flu.

1. Children and adults more than six months of age who have a long term health issue, including:
    - Chronic liver, kidney, cardiac, pulmonary, neurological diseases, respectively
    - Diabetes mellitus
    - Children getting a long term of salicylates therapy
2. Pregnant women in all trimesters
3. Immune-compromised people
4. Medical care staff and social workers who have close contact with an infected person

Therapeutic Strategies

Influenza is a major communicable pandemic disease with a global burden affecting all age groups, especially children and young people. Modern methods used to eradicate pandemic influenza infection include vaccines and antiviral agents such as adamantanes (rimantadine and amantadine) and NA inhibitors (laninamivir, peramivir, oseltamivir, zanamivir). Which oral adamantanes block the M2 ion channel of influenza A virus (IAV) that balances the acidity of the golgi complex microenvironment resulting in the uncoating of the virus. NA inhibitors prohibit the release of virion progeny after budding from the host cell.

Currently, Adamantanes have no action against influenza B virus (IBV) and NA inhibitors have shown activity against both IAV and IBV pathogens [95]. Available therapeutic weapons have limitations, including resistance to highly pathogenic viral strain, prohibitive cost, viral mutation, lack of availability of the desired vaccine due to the time lag between vaccine development and adverse side effects. Unfortunately, none of these drugs have, until recently, been fully capable of impressing on a new pandemic strain of H1N1 influenza to eradicate infection.

In addition to this, a new class of anti-influenza drug "baloxavir marboxil" has recently been licensed for the management of both influenza A and B viruses, a mode of action of this drug achieved by inhibiting the endonucleases of the viral polymerase enzyme complex. Although studies have shown that this antiviral compound has a significantly higher effect than Oseltamivir but is only authorized for use in Japan and the USA [96].

Therefore, the researchers also need to emphasize these traditional medicinal herbs, possess natural bioactive compounds that can be used to reduce flu disease and novel pandemic of H1N1 influenza in many geographical locations around the world [97]. Thus, the renovation of strategies for targeting viral surface glycoprotein is significant, because the viral protein is continuously changing its genetic makeup through antigenic variations and making it more potent. Therefore, these proteins are attractive targets for discovering and designing new classes of compounds to stop the progression of the disease. Alternative drugs with new either synthetic or natural bioactive agents are therefore urgently needed for disease mitigation and its related complications (Table 2).

Table 2 Influenza antiviral drugs currently available and under clinical trial [98, 99]

Drug	Generic name	Availability for use	Effective against	Specific Target	Status
Oseltamivir	Tamiflu®	Oral	IAV and IBV	Blocks NA protein and inhibit the release of virions after budding from the host cell	Approved
Zanamivir	Relenza®	Inhalation	IAV and IBV		
Peramivir	Rapivab®	Intravenous	IAV and IBV		
Amantadine Remantadine	Symmetrel Flumadine	Oral	IAV	Inhibits viral replication by blocking M2 membrane protein	Approved but currently not in use due to high resistance to IAV
Baloxavir marboxil	Xofluza®	Oral	IAV and IBV	Inhibit the cap-dependent endonuclease protein	Approved
Nitazoxanide	Nizonide	Oral	IAV (H1, H3, H5, H7) and IBV	Inhibits replication of virus by vitiate the trafficking of the HA protein from the endoplasmic reticulum to the Golgi complex	Under clinical trial phase III
DAS181	Fludase®	Oral/inhalation	(H1N1)pdm09, H3N2, H7N9, H5N1 and IBV	Remove silaic acid receptor from host and block the binding and entry of virus to the host cell	Phase I,II
T705	favipiravir	Oral	IAV, IBV and ICV	Inhibitor of RNA dependent RNA polymerase	Phase II, III

Conclusion

Through a comprehensive analysis, we have identified that children are at significantly higher risk of developing influenza infection as a result of all global pandemics. Therefore, the rate of medical facilities in hospitalization, treatment and ICU care must be increase year by year for children. Together with adult individuals in different settings, this in-depth review suggests that children may have played a significant role in facilitating the transmission of novel pandemics H1N1 influenza. The identification of children as a key "driver" group in propagating pandemic H1N1influenza is of much interest in the implementation of public health response strategies, including social distancing effort, useful antiviral drugs, and vaccination programs.

Author Contributions HKV conceived the study. YKR and NKV collected data. YKR, HKV,BLVKS and NKV wrote the manuscript. All authors have read and approved the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Consent for Publication All the authors have read the manuscript and have approved this submission.

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