Influenza B infection in children-A Review_R1

by Ramesh Bhat Y

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Influenza B infections in children- a review

Audio core tip

Influenza B outbreaks occur worldwide and young children exposed to influenza B tend to have higher disease severity compared with adults. The influenza B virus belongs to the Orthomyxoviridae family and has two distinct lineages; Victoria lineage and Yamagata lineage. The illness caused by influenza B is less severe than that caused by influenza A. Influenza B illness is less studied in children although its impact is substantial. Influenza B mostly causes mild to moderate respiratory illness in healthy children. However, the involvement of other systems, a severe disease especially in children with chronic medical conditions and immunosuppression, and mortality have been reported. Early treatment with antiviral agents decreases the severity of illness and hospitalization. Because of the enormous health and economic impact of Influenza B, these strains are included in vaccines. In this review, the disease burden, clinical manifestations, treatment, prognosis, and prevention of Influenza B illness in children have been discussed.

Abstract

Influenza B virus belongs to the Orthomyxoviridae family and has two antigenically and genetically distinct lineages; B/Victoria/2/87-like (Victoria lineage) and B/Yamagata/16/88-like (Yamagata lineage). The illness caused by influenza B differs from that caused by influenza A. The outbreaks of influenza B occurs worldwide and young children exposed to influenza B likely to have higher disease severity compared with adults. Influenza B mostly causes mild

to moderate respiratory illness in healthy children. However, the involvement of other systems, a severe disease especially in children with chronic medical conditions and immunosuppression, and rarely mortality, has been reported. Treatment with Oseltamivir or Zanamivir decreases the severity of illness and hospitalization. Because of the enormous health and economic impact of Influenza B, these strains are included in vaccines. Influenza B illness is less studied in children although its impact is substantial. In this review, the epidemiology, clinical manifestations, treatment, prognosis, and prevention of Influenza B illness in children have been discussed.

Keywords: children, Influenza B, hospitalization, oseltamivir, respiratory infections, severityIntroduction

Influenza is a major public health problem worldwide.[1-3] It is one of the most common respiratory infectious diseases. The influenza viruses belong to the Orthomyxoviridae family and contain a single-stranded RNA genome. There are three types of Influenza viruses A, B, and C based on different structural arrangements of internal nucleoprotein and matrix protein antigens. Influenza A (IFA) causes more severe illness and hence is well studied. Influenza B (IFB) is less studied in children although its impact is substantial. Influenza B has two antigenically and genetically distinct lineages, B/Victoria/2/87-like (Victoria lineage) and B/Yamagata/16/88-like (Yamagata lineage). Influenza C (IFC) is known to cause upper respiratory infection in younger children and community-acquired pneumonia. The severity of infection is less than that of IFA but more than that of IFB. C/Kanagawa/1/76- related lineages and C/Sao Paulo/378/82-related lineages are the IFC strains identified in the influenza seasons 2008–2009 and 2009–2010 in Milan.[4] Influenza B viruses have circulated worldwide

since 1983 causing outbreaks now and then.[5-8] Influenza B usually causes mild to moderate illness in healthy individuals including children. However, severe disease in children, the elderly, and individuals with chronic medical conditions have been reported. Serious illness leading to mortality although rare has been described. Worldwide, young children exposed to influenza B had higher disease severity compared with adults.[9-13] Antiviral agents decrease the severity of illness and hospitalization.[8] Because of the enormous health and economic impact of Influenza B, these strains are included in vaccines. In this review, the disease burden, clinical manifestations, differences between IFA and IFB illness, treatment, prognosis, and prevention of Influenza B illness in children have been discussed.

Epidemiology and disease burden

Influenza B was first identified in 1940 and the second lineage emerged in 1983. Since then Influenza B had frequent outbreaks.[1,3,5,6] Since 2001, both influenza B lineages have been cocirculating each influenza season. Children are more susceptible to infection. In particular, children under 5 years of age are more susceptible to influenza illness since they are an immunologically naïve population. IFB caused significant morbidity in children in the USA between 2004 and 2011, and in the UK during 2010-2011 seasons.[1-3,5,6] The influenza-associated morbidity among infants and young children may have been underestimated because other viral respiratory infections that present with fever also occur frequently during an influenza season. Annual influenza A and B attack rates among children aged 5 to 9 years reach 35%, compared with attack rates among adults which approach 13% for influenza A and 6% for influenza B. Outbreaks of influenza B occurred from November 2017 to April

2018 worldwide. The illness caused enormous health and economic consequences worldwide.[1-3, 5-7]

Mancinelli et al reported that among the IFB isolates, 91.54 % were the B/Yamagata/16/88 lineage and 8.45 % were the B/Victoria/02/87 lineage during the 2012–2013 influenza season in Italy.[2] The B/Yamagata/16/88 lineage was most prevalent in children 3–6 years old. They reported the median length of hospital stay of 3 days for IFB viral illness. An Indian report stated that estimated influenza-associated mortality in India was high among children aged less than 5 years apart from elderly people.[10]The studies on incidence, clinical burden, and economic impact of influenza B helped to include an additional B strain in the vaccine against influenza. A study involving IFB cases across 9 European countries reported wide variations of IFB cases during the years studied, 1998 to 2013.[5]

The Global Influenza B Study (GIBS) encompassing a total of 1.820.301 influenza cases between 2000 and 2018 from 31 countries reported 419,167 (23.0%) cases of influenza B.[14] Cases from the USA (54.1%) and Australia (25.3%) contributed the maximum to this study. In countries of the Southern hemisphere, influenza A epidemics peaked in July-September, and influenza B peaked in August-September. In Northern hemisphere countries, influenza A peaked in January-February compared to the influenza B peak in February-March. However, there were exceptions to this pattern in some countries. In most countries, influenza B/Victoria showed a unimodal curve with a peak below 10 years of age. B/Yamagata cases frequently followed a bimodal curve, with an earlier, larger peak below 10 years of age, and a smaller peak between 25 and 50 years of age. The timing of influenza A and B epidemics differ in

tropical countries. The epidemics can be highly heterogeneous with no consistent pattern in the timing of the different epidemics. B/Victoria occurs more frequently in tropical countries, while B/Yamagata occurs frequently in temperate climate countries of the Southern and Northern hemispheres.

Influenza B-viral characteristics

Influenza B viruses belong to the orthomyxoviridae family.[1,5,14] They are single-stranded RNA viruses. They are classified into two lineages: B/Yamagata and B/Victoria. IFB viruses are further classified into specific clades and sub-clades which are sometimes called groups and sub-groups. The B/Victoria clades include V1A and subclades include V1A.1, V1A.2, and V1A.3. B/Yamagata clades include Y1, Y2, and Y3. There are no subclades in B/Yamagata.

The IFB virus capsid is enveloped. Its virion consists of an envelope, a matrix protein, a nucleoprotein complex, a nucleocapsid, and a polymerase complex. The eight genome segments of IFB are encapsidated by the nucleoprotein. The polymerase complexes consisting of the three polymerase proteins PB1, PB2, and PA are located at the ends of the nucleocapsids. These helical capsids are encircled by the M1 matrix protein and a lipid bilayer envelope in which the virus surface glycoproteins haemagglutinin (HA) and neuraminidase (NA), as well as the M2 matrix protein, are embedded. Its 500 or more surface projections are made of hemagglutinin and neuraminidase.

IFB virus undergoes antigenic variation through genetic reassortment among co-circulating strains of different lineages and antigenic drift from cumulative mutations.[5, 14] IFB viruses generally change their genetic and antigenic

properties more slowly than IFA viruses. IFB virus HAs have a mutational rate about five times slower than that observed for IFA virus HAs. IFB virus is relatively vulnerable to damaging environmental impacts. Depending on humidity and temperature, it can survive up to several hours. In water, at low temperatures less than 20 °C they can survive up to several months. Influenza viruses are sensitive to lipid solvents and detergents.

Clinical features

Influenza B illness in children ranges from subclinical illness to complicated disease that affects multiple organs. In addition to its typical manifestation as respiratory tract and systemic signs and symptoms, IFB can present as croup, bronchiolitis, pneumonia, febrile disease mimicking bacterial sepsis, or, on occasion, CNS, cardiac, muscle, or renal complications.[1–3, 5-7, 11-17] IFB predisposes the infected children to bacterial superinfections. IFB viruses tend to persist across multiple seasons and exhibit complex global dynamics.[18] A peak between August and September has been observed in countries of the Southern hemisphere. In countries of the Northern Hemisphere, the peak occurs in February-March although exceptions do occur in certain countries. IFB epidemics tended to peak on average three weeks later than IFA epidemics during the winter period in temperate countries of both hemispheres.[14,18] An Indian study involving children found more cases from January to May with a peak in March.[12] The younger the child, the more difficult it is to distinguish influenza from other febrile illnesses based on clinical grounds alone.

IFB most often causes an uncomplicated respiratory infection with cough, fever, myalgia, chills or sweats, and malaise that persists for two to eight days. The onset is typically rapid. A minority of patients, especially young children,

and those with medical comorbidities will experience severe disease due to viral or secondary bacterial pneumonia with respiratory and multiorgan failure.

The highest frequency of IFB infections is said to occur in infants less than one year of age with a median age of the children of IFB of 4.2 years.[13] High fever especially an abrupt onset is common. Febrile convulsions are reported in 9% of children. Rhinorrhea and cough are the usual manifestations. Vomiting or diarrhea may occur in 25% of cases. Myalgia or myositis may be present in 15% and headache occurs in 25%. Pneumonia, otitis, and encephalitis may occur in a small percentage of children.

An Indian study involving IFB in children found upper respiratory tract infections in 78.5% cases followed by pneumonia in 19.6% and severe pneumonia in 1.7%.[12] The peak was observed in March. Male children predominated in the study.

Male predominance among IFB illness has been reported in other studies as well.[14-19] Gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting in IFB children are reported by Lennon et al.[16] IFB also affects the children with underlying malignancies such as lymphoma, leukemia, solid tumor, or tubulopathy. Encephalitis is a rare manifestation of IFB. A 6-year-old girl with acute influenza B virus encephalitis resulting in neurological sequelae was reported by McCullers et al.[20] IFB associated encephalitis, profound weakness, and response to oseltamivir were reported in a 10-year-old boy by John PS et al.[21]

Chi CY et al studied 118 cases of Influenza B in Taiwan with characteristics of Yamagata and Victoria strains.[19] They reported that children infected with Yamagata-like strains were more likely to develop lower respiratory tract infections. All cases of invasive disease belonged to this strain. Children infected with the Victoria-like group had the longest hospital stays associated with severe bacterial superinfection.

Host factors

Influenza is a major cause of morbidity and mortality in humans globally. Certain age groups are more susceptible to influenza. The children and elderly people are more vulnerable to influenza. IFB commonly affects younger children. Eski et al reported that children less than 5 years of age had a higher hospitalization rate (82.9%).[21] The strongest association between hospitalization and age was observed for children ≤2 years of age (63.6%) compared with other age categories (36.4%) by them.

IFB related childhood morbidity and mortality was more common in children with certain comorbidities. Underlying medical conditions such as asthma, neurologic deficits, or malignancies were documented in one-fourth of the children with influenza A or B.[13] Congenital heart disease, neuromuscular disease, immunosuppression, presence of neutrophilia, lymphopenia, severe bacterial infections, and late initiation of antiviral therapy were found to be independent risk factors for prolonged hospitalization for the patients who had influenza B-related lower respiratory infections. Prolonged hospitalization was more common in patients with comorbidities (24.3%) compared to the children without any comorbidities (10.4%).

How is Influenza B different from Influenza A?

Among Influenza viruses, Influenza A virus causes more severe disease. Certain differences in median age, clinical manifestations, the severity of illness, risk factors, and length of hospitalization days were observed between IFA and IFB in various studies. [2, 6, 11, 15] Peltola et al reported that the median age of the children with IFA was 2.0 years and that of the children with IFB was 4.2 years. [13] Infants accounted for 27% of the children with IFA and 24% of those with IFB. Boys were overrepresented in both IFA and IFB infected children. Underlying medical conditions were detected in 26% of the children with IFA and 34% of those with IFB. Fever is a common symptom for both IFA and IFB affected children. High fever and rhinorrhea were more common in IFA than in IFB. Respiratory symptoms were more prevalent in patients affected by IFA than by IFB.

Mancinelli et al observed that IFA was more common in children less than one-year-old, where they can cause more severe infections and IFB was more common in school-age children.[2] The length of stay in children with IFA was significantly higher than those infected with IFB. The median length of stay was 5 days (range: 0–59) for IFA and 3 days (range: 0–116) for IFB. IFB children mostly had a fever <38°C. An Indian study also observed more IFB cases in the older age group.[12] Respiratory symptoms dominate in IFA children. Lennon et al found gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting more commonly with IFB than IFA infection.[16] Children with IFB were more likely than those with IFA to be diagnosed as upper respiratory tract infection, myositis, and gastroenteritis. Influenza children with underlying malignancies such as lymphoma, leukemia, solid tumor, or tubulopathy were more susceptible to IFB infection.

Variables

Influenza A

Influenza B

Epidemiology

Epidemic/Pandemic

Epidemic peak *

Southern hemisphere

Northern hemisphere

Constitute about 75% of total influenza

Causes both epidemic and pandemic

July-September

January-February

Constitute about 25% of total influenza

Causes epidemic

August September

February-March

Virology

Family

Type

Subtypes/lineages

Common types

Pandemic strain

Infection

Belong to Orthomyxoviridae

Single-strand RNA virus

18 H subtypes and 11 N subtypes

A(H1N1)[1] and A(H3N2)

A(H1N1)[2]pdm09 virus

Humans, pigs, horses, wild birds, etc.

Belong to Orthomyxoviridae

Single-strand RNA virus

Two lineages: B(Victoria) and B (Yamagata)

Victoria and Yamagata lineages

Only in humans (may be in seals)

Host factors (children)13

age (years) (median)

Infants

School-age

Gender

2.0

Commonly affected

Can be affected

Male predilection

4.2

Less commonly affected

Commonly affected

Male predilection

Clinical features 13,16

Fever

Febrile convulsion

Rhinorrhea

Underlying medical

conditions

Length of hospital

Stay (median)

Gastrointestinal

symptoms (abdominal

pain, vomiting,

diarrhea)

Myositis

Otitis media

High

About 5.4%

Common

Not so common (26%)

5 days

Less common

1.1%-6%

26%

< 38.50 C

About 10.7%

Common

More common (34%)

3 days

More common

4.5%-15%

19%

Lab parameters

Leucopenia

Leucocytosis

Elevated CRP

Less common (8%)

8%

31%

More common (19%)

7%

15- 46%

Treatment

Oseltamivir

Zanamivir inhalation

Effective

Effective in ≤5 years of age

Effective

Effective in ≤5 years of age

Prognosis

Complications

Good

May occur

Good

In young children/ having comorbidities

Vaccine (Quadrivalent)

Effective

Effective

Table 1. The differences between Influenza A and Influenza B illness in children 2, 13, 15, 16Laboratory Tests

Several different approaches are currently available for the diagnosis of influenza infections in humans.[23-25] These include viral isolation in cell culture, immunofluorescence assays, nucleic acid amplification tests (NAT), and immunochromatography based rapid diagnostic tests.[23] Rapid molecular assays are the preferred diagnostic tests because they can be done at the point of care. They are more accurate and give results fast.[24]

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) is the most powerful NAT approach for the identification of influenza viruses in most diagnostic labs around the world. These tests are far more sensitive compared with the antigen-based serological tests. They can detect viruses much earlier in clinical samples. A variety of different NATs are currently available for the diagnosis of influenza infections in humans. These include RT-PCR, ligase chain reaction, sequencing-based tests including pyrosequencing, next-generation sequencing (NGS), DNA microarray-based tests, nucleic acid sequencing-based amplification (NASBA), loop-mediated isothermal amplification-based assay (LAMP), simple amplification-based assay (SAMBA), transcription-mediated amplification, strand displacement amplification, etc. [23] Most of these tests take 2 to 4 hours to complete. They demonstrate higher sensitivity and specificity compared with antigen-based tests. RT-PCR, a gold standard assay, for influenza diagnosis involves three essential steps: extraction of viral RNA from clinical specimens; reverse transcription of viral RNA to a single-stranded cDNA using the enzyme reverse transcriptase, and

amplification of the PCR product is coupled to fluorescent detection of labeled PCR products.[23, 24]

Nasopharyngeal and nasal swab samples should be obtained from influenza affected children and transported to the laboratory in a viral universal transport medium. Samples of the throat and nasal swabs, nasopharyngeal aspirate, bronchoalveolar lavage, and sputum may also be taken in different clinical situations. The samples should be either processed immediately or stored at –80 °C for up to two days before testing. Nucleic acid extraction and reverse transcription should be performed initially. Samples positive for IFB are further characterized by genotyping analysis to identify the subtype; the B/Yamagata/16/88 and B/Victoria/02/87 lineages. Different primers are used to identify Victoria lineage and Yamagata lineage.[23-25]

Other laboratory tests include white blood cell (WBC) counts and serum C-reactive protein (CRP) levels. Determinations of WBC counts and serum CRP levels may be helpful in the detection of bacterial coinfections because these values are low in patients with uncomplicated IFB. A decreased WBC count of less than 4000/mm3 or more than 15 000/mm3 can occur in about 10% of children with IFB.[13] Leukopenia observed in association with IFB should not prompt any further evaluation, because influenza is known to cause lymphopenia. IFB is more clearly associated with leukopenia than IFA. One study reported an elevated CRP level in 46 % of IFB children.[2]

Treatment

The children affected with IFB need supportive care and antiviral agents.[26-30] The neuraminidase inhibitors are effective drugs for influenza B illness in

children. Oseltamivir is orally bioavailable in children aged 1 to 12 years and is efficiently metabolized to the active carboxy metabolite. Pharmacokinetic modeling in children indicated that a dose of oseltamivir 2 mg/kg/dose twice a day would be safe and effective.[29] The oseltamivir carboxylate is primarily eliminated by renal excretion.

Early administration of oseltamivir can reduce the risk of influenza B virus-associated pneumonia.[8] In field[3] trials, the greatest benefit from anti-influenza drugs is gained if therapy is started within 48 h after the onset of symptoms.[13, 28, 29] Whitley et al in their randomized controlled study reported that among 144 children infected with influenza B, subgroup analyses showed a significant reduction in the median duration of fever, cough, and coryza (placebo 100 h, oseltamivir 73 h; P = 0.01) and other symptoms in oseltamivir group.[29] Treatment with oseltamivir also caused a rapid decline in viral shedding. Oseltamivir significantly reduced the occurrence of secondary complications during the study, notably otitis media. It is well tolerated. Vomiting may be observed in a few children. Hypothetically oseltamivir treatment might reduce the likelihood of the spread of influenza to close contacts as well. Matheson et al also found Oseltamivir being effective in reducing the incidence of secondary complications.[30] Sato M et al in Japan found the effectiveness of oseltamivir in IFA and IFB, and the benefit increased for younger children.[26] On the other hand, Suzuki and Ichihara found oseltamivir being less effective against IFB than in IFA.[27] If influenza infection is suspected, initiation of antiviral treatment without waiting for laboratory confirmation is suggested for the children with comorbidities and unvaccinated children younger than 6 months and patients.[22]

The main advantages of neuraminidase inhibitors compared with amantadine and rimantadine, are fewer adverse effects, activity against both IFA and IFB, and rare resistance. Zanamivir is another drug effective in shortening the duration and severity of influenza. A 5-day course of twice-daily inhaled zanamivir, 10 mg, was compared with placebo in the treatment of symptomatic IFB among children 5 to 12 years of age.[28] Reduction in the duration of symptoms of IFB has been demonstrated in children 5–12 years of age who were receiving inhaled zanamivir.

Prognosis

Prognosis is generally good for children affected by IFB. Some of the affected children may require hospitalization for 2 to 8 days. The average length of hospital stay of 3 days has been documented.[2] The majority (78.5%) having upper respiratory infections and recovering well without any complications, pneumonia in 14.2% children aged greater than five years, and 5.3% children[4] between one to five years have been documented.[12] The disease tends to be severe in young children and those with comorbidities. Mortality from IFB in children remains low.

Vaccination

World Health Organization and CDC recommend that children between 6 months and 5 years should be vaccinated against IFA and IFB. Inclusion of this age category in vaccination recommendations may help avoid hospital admissions for influenza. Since there is no licensed influenza vaccine for children younger than 6 months, alternative strategies including maternal vaccination during pregnancy and household vaccination are likely to reduce the burden of influenza.[22] Multiple influenza vaccine

manufacturers have initiated studies to support the approval of quadrivalent seasonal influenza vaccines that include an additional B strain to provide immunity against both lineages of influenza B. Influenza vaccine including B strain is likely to offer benefit in children with chronic pulmonary, cardiac, or renal disease, diabetes mellitus, or immunosuppression, or to those receiving long-term salicylate treatment.

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7.	~~Daleno~~ → Delano	Misspelled Words	Correctness
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