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Influenza in Children

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Influenza poses a significant disease burden on children worldwide, with high rates of hospitalization and substantial morbidity and mortality. Although the clinical presentation of influenza in children has similarities to that seen in adults, there are unique aspects to how children present with infection that are important to recognize. In addition, children play a significant role in viral transmission within communities. Growing evidence supports the idea that early influenza infection can uniquely establish lasting immunologic memory, making an understanding of how viral immunity develops in this population critical to better protect children from infection and to facilitate efforts to develop a more universally protective influenza vaccine.

Infection with influenza is exceedingly common in children worldwide. Globally, the incidence of influenza in children under the age of 5 is estimated to be 90 million cases per year (Nair et al. 2011), with the incidence in children in the United States estimated at 19/1000 per year (Fowlkes et al. 2014). Less than 10% of children less than 5 yr of age have a laboratory-confirmed influenza health-care visit each year, and an estimated 6%–12% of U.S. children seek care for influenza or an influenza-related illness each year (Neuzil et al. 2002; Poehling et al. 2006). Young children make up the largest proportion of patients seeking influenza-related care, with children less than 5 yr of age hospitalized because of influenza and related conditions at a

rate of 1000 per 100,000 person-years (Poehling et al. 2006; Caini et al. 2018). Globally, an estimated 28,000 children less than 18 yr of age die from influenza-related lower respiratory tract infections each year, with the majority of these deaths occurring in children less than 4 yr of age (Troeger et al. 2019). In the United States, the overall cumulative mortality of children with influenza is 0.15 deaths per 100,000 children, with a higher cumulative mortality of 0.66 deaths per 100,000 children in children less than 6 mo of age (Shang et al. 2018). Low-to-middle-income countries (LMICs) are disproportionately affected by influenza-related mortality. The case fatality rate for children with influenza is up to 15 times higher in LMICs than in

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developed countries, and an estimated 99% of influenza-related deaths among children younger than 5 yr of age occur in LMICs (Nair et al. 2011).

Influenza infection in children also poses a socioeconomic burden for both children and families. Almost all school-aged children with influenza miss at least a day of school, with influenza infection leading to the highest average days of school missed compared with other common childhood acute respiratory illnesses such as respiratory syncytial virus, human metapneumovirus, parainfluenza virus, and coronavirus (Principi et al. 2003; Ambrose and Antonova 2014; McLean et al. 2017). Furthermore, around one-half of the parents of children with influenza miss at least a day of work, and many others must hire caregivers for sick children. Children with influenza often visit health-care providers once or more during the course of their illness, which may incur additional costs for the family and place an added burden on a country's health-care system (Ambrose and Antonova 2014).

Assessing the true burden of influenza in the pediatric population is difficult for several reasons. For one, a large proportion of the burden of influenza in children is not from the primary infection, but rather from secondary infections, exacerbations of existing chronic diseases such as asthma or other complications. These complications may not be attributed to influenza even if influenza infection was the initial causal pathogen behind the presentation (Gordon and Reingold 2018). Delayed presentation to health-care facilities combined with a reliance on molecular testing can also lead to underestimations of burden. Indeed, a recent study that combined molecular and serological testing with wide testing criteria indicated that the burden of severe influenza in infants may be twice that of current global estimates (Thompson et al. 2019). In addition, maternal influenza infection is associated with increased maternal morbidity and mortality, as well as increased occurrence of premature and small-for-gestational-age births. These events may have lifelong health consequences for the child, but assigning causality to influenza is difficult and rarely done (Dodds et al. 2007;

Omer et al. 2011). Even in cases in which influenza virus is confirmed with laboratory testing, the high prevalence of other respiratory viruses in the pediatric population can make the determination of a precise viral etiology difficult (Gordon and Reingold 2018). All of these factors lead to a pediatric influenza burden that is likely underestimated, especially in LMICs in which even the overall incidence of influenza is generally poorly characterized (Widdowson and Monto 2013).

CLINICAL PRESENTATION

The clinical presentation of influenza in children shares many features with adult influenza. Classically, a child will present with a combination of subjective fever, headache, cough, pharyngitis, and coryza, as well as general malaise, myalgias, and muscle fatigue (Table 1) (Poehling et al. 2006; Silvennoinen et al. 2009; Ruf and Knuf 2014). Clinical signs of influenza include a temperature of $>37.8^{\circ}\text{C}$ (100°F), clear nasal discharge, and erythematous nasal and pharyngeal membranes without exudate. The lungs are typically clear to auscultation in primary influenza infection, although scattered rhonchi and crackles can occasionally be heard. In addition to these shared features, there are features of influenza in children that are rarely experienced in adult patients. Cervical lymphadenopathy is much more frequently seen in influenza-positive children than adults, and children are more like-

Table 1. Relative occurrence of influenza signs and symptoms in medically attended children

Subjective fever	Extremely common
Temperature $\geq 38^{\circ}\text{C}$	Very common
Cough	Very common
Rhinorrhea	Very common
Coryza	Very common
Headache	Common
Myalgia	Uncommon
Vomiting/diarrhea	Common
Rhonchi/crackles	Uncommon

Approximate prevalence of symptoms/signs in children with influenza: uncommon, 0%–30%; common, 30%–60%; very common, 60%–90%; and extremely common, 90%–100%.

ly to have a higher temperature than adults. Furthermore, a significant proportion of children experience gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain. The pathogenesis of these symptoms is not well-established. Although fecal shedding of influenza virus may be observed, the relationship between fecal shedding and gastrointestinal symptoms is unclear and there is little evidence for direct influenza-mediated damage in the gastrointestinal tract (Minodier et al. 2015).

Although influenza can be devastating as a primary infection, the most feared complications in children typically stem from secondary manifestations of influenza (Table 2). A study conducted in Sweden reported that 41% of influenza-positive children less than 18 yr of age experienced some form of influenza-related complication (Bennet et al. 2016). The most common complications in children are primary viral or secondary bacterial pneumonia, seizures, other secondary bacterial infections such as sinusitis or acute otitis media, and exacerbation of existing respiratory issues such as asthma (Neuzil et al. 2000b; Zambon 2013; Bennet et al. 2016). Rarer but potentially devastating complications include myalgia with elevated creatinine kinase, Guillain–Barré syndrome (an autoimmune condition characterized by demyelination and loss of function of peripheral motor neurons leading to ascending muscle weakness and paralysis) and Reye’s syndrome (Verity et al. 2011; Vellozzi et al. 2014; Sellers et al. 2017). Encephalitis/encephalopathy can also occur, with >80% of cases of influenza-associated encephalitis/encephalopathy occurring in children less than 5 yr of age, often with severe resulting morbidity or even mortality (Kasai

et al. 2000; Britton et al. 2017). Although up to 73% of Reye’s syndrome cases are preceded by influenza, because of the nearly absolute contraindication of aspirin use in children, reports of Reye’s syndrome have decreased to one to two cases per year in the United States (Chapman and Arnold 2019).

Many influenza symptoms are nonspecific and may be associated with different respiratory illnesses in children. This, combined with the variance in presentation from completely asymptomatic to severe illness leading to death, makes diagnosis of influenza difficult (Zambon 2013). For example, a study in Nashville, Tennessee found that only 17% of children with laboratory-confirmed influenza were given a diagnosis of influenza by their physician in the outpatient setting (Poehling et al. 2006). This necessitates the exploration of clinical features that are more highly associated with influenza than other common respiratory illnesses. A study in Nicaragua found that both rhinorrhea and nasal congestion are observed significantly more in febrile children with laboratory-confirmed influenza than in febrile children with noninfluenza illnesses (Gresh et al. 2016). Furthermore, the combination of cough and fever within 48 hr of symptom onset is highly predictive of influenza, as is the concurrent occurrence of cough, headache, and pharyngitis (Monto et al. 2000; Friedman and Attia 2004). Integration of these clinical models as well as further development of point-of-care diagnostic tools may help improve the detection and diagnosis of influenza in children.

There appear to be no significant differences in the clinical presentation of different influenza subtypes, such as seasonal influenza A/B or between seasonal influenza and the 2009 pandemic. Although neurologic complications may be more common in 2009 pandemic influenza, the underlying symptomology is consistent with that of seasonal influenza (Calitri et al. 2010). Age-adjusted rates of complications such as acute otitis media, pneumonia, and sinusitis, as well as metrics of severity such as hospitalizations, intensive care unit (ICU) admissions, mechanical ventilation rates, and absenteeism from school, have not been found to be signifi-

Table 2. Relative occurrence of influenza complications in children

Acute otitis media	Common
Bacterial pneumonia	Uncommon
Primary viral pneumonia	Uncommon
Sinusitis	Uncommon
Seizures	Uncommon
Encephalitis	Rare

Prevalence of complications in children with influenza: rare, <1%; uncommon, 1%–5%; and common, 5%–20%.

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cantly different between influenza A and influenza B (Friedman and Attia 2004; Irving et al. 2012; Silvennoinen et al. 2015). Although population-level differences in complications may be present between seasonal and 2009 pandemic influenza, this can be attributed to different patterns of age-group susceptibility rather than underlying differences in the clinical presentation (Silvennoinen et al. 2015).

INFLUENZA TRANSMISSION

Children, especially those who are of elementary school age and younger, are thought to be primary drivers of influenza transmission within communities. Although adults have a role in transmitting influenza from one geographic location to another because of more frequent travel, children are thought to be the primary facilitators of influenza spread within a given community (Russell et al. 2008; Jernigan and Cox 2013; Worby et al. 2015). The critical role of children in transmitting influenza is also supported by studies showing that vaccination programs targeting school-aged children simultaneously reduce influenza infections and influenza-related primary care physician visits, emergency department visits, and hospitalizations in the unvaccinated adult population (Weycker et al. 2005; Baguelin et al. 2013; Pebody et al. 2015; Wang et al. 2016). In addition, many studies have shown that school closures during both pandemic and epidemic influenza outbreaks reduce transmission of influenza in the entire community, not just among school-children (Cauchemez et al. 2008; Jackson et al. 2013; Ali et al. 2018). Transmission of seasonal influenza from an index case to other members of a household, or secondary influenza transmission, is more likely to occur if the index case is a child when compared with adult index cases (Viboud et al. 2004; Tsang et al. 2015). Notably, this increased influenza transmissibility observed in children may depend on the influenza strain; some studies, particularly studies of 2009 pandemic influenza, found no association between age of the index case and likelihood of transmission (Cauchemez et al. 2009). Literature is also mixed regarding differences in char-

acteristics of transmission between influenza A and B and the selective vulnerability, if any, that children have to different strains. Influenza B is generally considered to be more common in children and more difficult to transmit to adults when compared with influenza A (Monto and Kioumehri 1975; Nair et al. 2011; Gordon et al. 2018), however, other evidence suggests that influenza A and B have very similar profiles of transmissibility in both children and adults (Azman et al. 2013).

There are several proposed explanations for the critical role of children in influenza transmission within communities. In addition to showing increased transmissibility of seasonal influenza, preschool and school-age children are themselves more susceptible to secondary transmission of influenza than adult household members (Viboud et al. 2004; Cauchemez et al. 2009; Casado et al. 2014; Gordon et al. 2018). The observation that children are more likely to become infected with influenza and, once infected, are more likely to transmit the infection to other household members helps explain the central role of children in the circulation of influenza in communities. This, combined with the fact that children spend lots of time with extra-household contacts in close-quarter locations such as schools and day-care centers, creates an environment where influenza can quickly propagate through a pediatric population and then transmit the virus to adult family members and other community members (Viboud et al. 2004; Mossong et al. 2008). Furthermore, young children are more likely to practice poor hand hygiene and engage in practices such as touching one's nose, eyes, and mouth and putting objects in one's mouth. Each of these behavioral components may bolster the virus's ability to get from child to child or child to adult (Zomer et al. 2015).

In addition to these social and behavioral factors, observed differences in the duration and timing of viral shedding between children and adults help explain the role of children in influenza transmission. There is evidence that children begin to shed influenza virus for a day or more before becoming symptomatic (Frank et al. 1981; Ng et al. 2016). This contrasts with

adults, in which presymptomatic viral shedding is shorter and less common. This finding theoretically explains some of the increased transmissibility observed in children, as there is a window of time in which a potentially infectious child may be engaging in typical activities such as attending school or day care while infectious. Furthermore, younger children tend to have a longer duration of viral shedding compared with older children and adults, representing an increased amount of time in which viral transmission can occur (Ng et al. 2016; Maier et al. 2018). Further investigation is needed to pinpoint the mechanism for these observations, although the relatively immunologically naive immune system of children has been posited as a possible explanation (Monto 1999; Viboud et al. 2004; Ng et al. 2016). Children may also have finer aerosol particles ($\leq 5 \mu\text{m}$) that may contain a higher density of viral particles (Yang et al. 2011; Milton et al. 2013). It is thus plausible, although not empirically shown, that exhalation of a higher proportion of fine aerosol particles with increased viral density contributes to increased infectivity (Schwarz et al. 2010; Bake et al. 2019).

INFLUENZA PREVENTION

Currently, annual vaccination is the best way to protect children against seasonal influenza virus infection. Recommendations in the United States are for vaccination of all individuals 6 mo of age and older with inactivated influenza vaccine (IIV), with administration of live attenuated influenza vaccine (LAIV) an option, but only in children >24 mo of age owing to a reported increased risk of post-LAIV wheezing in infants (Belshe et al. 2007; Grohskopf et al. 2019). Although several other developed countries, including Canada, also recommend universal vaccination, most countries recommend vaccination for high-risk children only. Children less than 9 yr of age initially receive a priming dose of vaccine followed by a booster dose of vaccine at least 28 d later as they may be relatively immunologically naive to this virus, with yearly vaccination recommended thereafter (Grohskopf et al. 2019). Because of the circulation of

two antigenically distinct lineages of influenza B (Victoria lineage and Yamagata lineage) in humans, many influenza vaccines currently approved for use in children are now quadrivalent (Ambrose and Levin 2012; Paul Glezen et al. 2013). Overall influenza vaccination coverage in children remains suboptimal even though children are considered an at-risk population, with substantial variability by age, location, and season. Between the 2010–2011 and 2017–2018 influenza seasons in the United States, vaccination coverage ranged between 63.6% and 70% for children 6 mo to 4 y of age, but dropped to 33.7% to 48.8% among teens (Centers for Disease Control and Prevention 2019). Strikingly, vaccination coverage in 358 laboratory-confirmed influenza-associated pediatric deaths between July 2010 and June 2014 was at 26%, with only 31% of even those with high-risk conditions appropriately vaccinated (Flannery et al. 2017). This highlights the importance of efforts to increase overall influenza vaccination rates among children.

Although influenza vaccination is currently the most effective method of preventing seasonal influenza infection, vaccination has significant limitations in the pediatric population. IIV is not licensed for children less than 6 mo of age and is poorly immunogenic in young children, requiring a second booster dose with first vaccination. Adjuvants have been used to increase the effectiveness of IIV, with both MF59 and AS03 shown to increase immunogenicity through multiple mechanisms, including improved innate immune activation, B-cell reactivity, and CD4 T-cell recruitment (Zedda et al. 2015). Studies to date have shown the safety of MF59-adjuvanted IIVs in children (Vesikari et al. 2018; Patel et al. 2019), with an MF59-adjuvanted seasonal trivalent influenza vaccine now approved for use in Canada. Although this increased immunogenicity offers great potential benefit, the association between an AS03-adjuvanted monovalent 2009 pandemic influenza vaccine and narcolepsy during the 2009 H1N1 pandemic may have slowed more widespread adoption of these vaccines for use in children (Miller et al. 2013; Verstraeten et al. 2015; Sarikanen et al. 2018).

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In addition to poor immunogenicity, the lack of influenza vaccine licensure in infants less than 6 mo of age is particularly problematic as infants are at the highest risk for severe influenza infection with high hospitalization rates (Izurieta et al. 2000; Neuzil et al. 2000a). Pregnant and postpartum women are also at higher risk for severe influenza illness and complications; thus, it is recommended that all women who are or will be pregnant during the influenza season receive IIV as soon as it becomes available (Committee on Obstetric Practice 2018). Studies have shown that anti-influenza antibodies cross the placenta and result in higher hemagglutination inhibition (HAI) titers in cord blood compared with placebo recipients (Madhi et al. 2014), with lower rates of documented acute lower respiratory tract infection, influenza infections, and influenza-related hospitalizations in infants when mothers are vaccinated during pregnancy (Zaman et al. 2008; Benowitz et al. 2010; Nunes et al. 2017). Although vaccination at any point during pregnancy is recommended, infants had higher antibody titers against the A(H1N1) virus when vaccinated during the second or third trimester and >4 wk before delivery (Zhong et al. 2019). Vaccination of breastfeeding mothers with IIV as opposed to LAIV resulted in significantly higher serum HAI titers as well as IgG and IgA levels in breast milk, suggesting that IIV may also be the preferred vaccine in breastfeeding mothers (Brady et al. 2018).

Unlike IIV, LAIV is not recommended for children less than 2 yr of age or during pregnancy. However, despite these limitations, LAIV may offer some advantages in the pediatric population. Early studies of LAIV, many of which were conducted before the U.S. recommendation for universal pediatric influenza vaccination, showed improved vaccine efficacy in children compared with IIV, including improved protection against antigenically drifted strains (Belshe et al. 2000a, 2007; Rhorer et al. 2009). Together, accumulated data ultimately led to the preferential recommendation for LAIV use in children in the 2014–2015 influenza season (Grohskopf et al. 2014). However, following replacement of the previously circu-

lating A(H1N1) strain with the 2009 pandemic strain, data showing decreased protection against the 2009 pandemic vaccine component began to emerge (Chung et al. 2019). Multiple factors may have contributed to this poorer performance, with manufacturer evidence suggesting decreased replicative fitness of the A/Cali-fornia/7/2009 and the subsequent A/Bolivia/559/2013 strains to be a primary contributor. For this reason, LAIV was not recommended for use in the United States in 2016–2017 and 2017–2018 (Grohskopf et al. 2016), but was again recommended in 2018–2019 with introduction of the A/Slovenia/2903/2015 H1N1 viral strain postulated to have greater shedding and immunogenicity (Grohskopf et al. 2018). However, it is of note that the U.S. findings of low effectiveness in the 2015–2016 season differed from findings in other countries, and other countries, including Canada, continued to recommend LAIV for children (Tam 2018). These data highlight the need for a better understanding of LAIV correlates of protection and the impact of preexisting immunity on vaccine effectiveness.

PEDIATRIC HOST RESPONSE TO INFLUENZA INFECTION

Immunity in infants differs both quantitatively and qualitatively from that in adults, with data interpretation further complicated by the presence of circulating maternal antibody. Most notably for influenza, production of Th17-associated effector cytokines on Toll-like receptor (TLR) signaling peaks postnatally in term infants and then declines over the first 2 yr of age, whereas Th1-supporting cytokines, including IL-12p70 and IFN- γ , slowly increase throughout childhood (Yerkovich et al. 2007; Corbett et al. 2010). Early in life, there is also an elevated frequency of cells with a phenotype consistent with T_{reg}, with 10%–30% of CD4 T cells expressing CD25 and FOXP3 in the first 2 yr of life (Thome et al. 2015). Further, the influenza-specific B- and T-cell repertoires in infants and young children contain a greater frequency of naive cells, with many fewer influenza-specific cells with a memory phenotype

secondary to the limited influenza encounters through either annual vaccination or natural infection in this age group. This contrasts markedly with older children and adults, in which there are preexisting populations of influenza-specific memory cells that can target conserved epitopes (Kreijtz et al. 2007; Lee et al. 2008; Koutsakos et al. 2019) and provide non-sterilizing immunity on reinfection (McMichael et al. 1983; Wilkinson et al. 2012; Sridhar et al. 2013). Because the responding memory cells have a significant advantage in terms of both precursor frequency and the threshold of activation required to induce a response (Croft et al. 1994; London et al. 2000; Rogers et al. 2000; von Essen et al. 2012), the induction of an adaptive immune response in young children is likely delayed. This may contribute to higher levels of viral replication and age-dependent differences in susceptibility to influenza virus infection. These important immunologic differences underscore the need to evaluate immunity in infants without application of typical adult conventions, keeping in mind that the age on infection of a given child could substantially impact the nature of the ensuing immune response.

Following infection, influenza virus primarily targets and infects respiratory epithelial cells of children and adults via the viral hemagglutinin (HA) protein, and a vigorous inflammatory response ensues with activation of multiple pattern recognition receptors, including TLRs, the retinoic acid-inducible gene (RIG)-like receptors, and the nucleotide-binding oligomerization domain (NOD)-like receptors (Coates et al. 2015). This leads to a robust innate immune response with activation of neutrophils, monocyte recruitment, and maturation of dendritic cells, resulting in decreased viral replication and instruction of the developing adaptive immune response (Wu et al. 2011; Iwasaki and Pillai 2014; Pulendran and Maddur 2015). Following initial influenza infection of a child with no previous influenza exposures, naive influenza-specific CD4 T cells and CD8 T cells are activated and expand (Chen et al. 2018; Nüssing et al. 2018). In mouse models, lung tissue-resident memory CD8 T cells (T_{rm}) established postinfection are poised to rapidly respond on

reinfection and have a key role in immune protection (Wu et al. 2014; Pizzolla et al. 2017). These T_{rm} cells are present in healthy adult lung tissue (Kumar et al. 2017; Pizzolla et al. 2018); however, when this population of cells is established following childhood influenza infection is not yet known. Interestingly, murine models suggest T_{rm} may be less well-generated in infancy, providing another potential immunologic mechanism for the increased susceptibility of young children to influenza (Zens and Farber 2016).

Early infection with influenza virus also establishes a B-cell response, with a detectable memory B-cell response developing in children as young as 2 yr of age (Sasaki et al. 2007). On infection, B cells specific for a wide diversity of influenza viral proteins respond, with antibodies directed against epitopes to surface and internal proteins, including broadly protective epitopes within the HA stalk (He et al. 2015; Tesini et al. 2019). These cells persist and can be recalled on challenge with a divergent influenza strain (Wrammert et al. 2011; Margine et al. 2013). It has been well-established that on repeated exposure to closely related influenza strains epitopes within the HA head are immunodominant (Andrews et al. 2015; Lee et al. 2016); however, whether stalk reactive antibodies are relatively enriched for in the pediatric population has yet to be determined.

Although the preferential boosting of antibodies specific for earlier viral strains on encounter with an antigenically drifted influenza virus, or “original antigenic sin,” was first described decades ago (Davenport et al. 1953; Francis 1960; Fazekas de St. Groth and Webster 1966), recent data has indicated that influenza strains originally encountered in childhood may establish long lasting protection against novel influenza strains belonging to the same HA group (Gostic et al. 2016). This cross-subtype protection has been termed “immunologic imprinting,” and there is now an appreciation for its role in both establishing lasting anti-influenza protective immunity and in shaping lifelong responses to influenza vaccination (Reber et al. 2016; Nachbagauer et al. 2017; Nuñez et al. 2017; Kosikova et al. 2018).

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MECHANISMS OF INFLUENZA VACCINE-ASSOCIATED PROTECTION FOLLOWING IIV

IIV have been shown to be effective in both infants and young children (Jefferson et al. 2018), with protective antibody levels and the generation of antibody-secreting cells in even former premature infants vaccinated at 6–17 mo of age (Groothuis et al. 1992; D’Angio et al. 2011, 2017). This protection is predominately through stimulation of a HA-specific neutralizing antibody response quantified using the serum HAI antibody titer as a correlate of vaccine-induced protection. In adults, an HAI titer of >1:40 is typically considered protective (de Jong et al. 2003; Treanor and Wright 2003; Ohmit et al. 2011), but higher HAI titers may be necessary to achieve similar levels of protection in children (Black et al. 2011).

In addition to B-cell responses, IIV induces CD4-T-cell responses even in very young children. When a population of IIV vaccinated children less than 3 yr of age with no history of documented influenza infection was examined, influenza-reactive circulating CD4 T cell could be detected. Interestingly, the immunodominance hierarchy of this response reflected the composition of IIV, with detectable responses to the HA proteins but little reactivity to the internal virion proteins NP and M1 (Shannon et al. 2019). Vaccination is also able to activate a population of T_{fh}, with these cells detectable in the peripheral blood of older children. This shows the ability of childhood IIV vaccination to activate T_{fh} that then can provide cognate help to B cells (Bentebibel et al. 2013).

MECHANISMS OF INFLUENZA VACCINATION FOLLOWING LAIV

In contrast to IIV, the correlates of LAIV-induced immunological protection remain unclear, with traditional measurements of immunity failing to correlate with protection from subsequent LAIV challenge (Wright et al. 2016). Studies have established that the systemic neutralizing antibody titer is generally lower following immunization with LAIV as opposed to IIV

(Treanor et al. 1999; Sasaki et al. 2007; Nakaya et al. 2011; Ohmit et al. 2011; Cao et al. 2014), with higher LAIV-induced HAI titers associated with younger age and baseline seronegativity (Coelingh et al. 2014). Despite this modest serum HAI response, early studies of LAIV showed improved vaccine efficacy in children, including protection against antigenically drifted strains (Belshe et al. 2000a, 2007; Rhorer et al. 2009). Preferential induction of local as opposed to systemic immunity (Panapasa et al. 2015; Mohn et al. 2016; Jegaskanda et al. 2018), including mucosal antibody responses (Belshe et al. 2000b; Ambrose et al. 2012; Mohn et al. 2016), increased innate immune activation (Zhu et al. 2010; Nakaya et al. 2011), and more robust CD4 and CD8 T-cell responses (He et al. 2006; Hoft et al. 2011) may account for the effectiveness of LAIV in children despite lower HAI titers. Despite these potential advantages, the need for vaccine viruses to infect and undergo limited replication means that vaccine effectiveness may be impacted if preexisting host immunity neutralizes or curtails replication of vaccine virus (Ilyushina et al. 2015). This may account for the improved efficacy of LAIV in seronegative children as compared with adults and could potentially result in reduced immunogenicity in children vaccinated annually.

RESEARCH GAPS

Although great strides have recently been made in understanding the presentation, transmission, and immunity to influenza in children, exciting questions remain. Further research is needed to address how host and viral factors affect disease severity and predispose to secondary infections in infants and children. In addition, although it is thought that children are a primary driver of disease transmission, the mechanism by which host factors, such as smaller airway size and clinical features, impact transmission needs to be determined. Another area of emerging research is the mechanism underlying the greater durability of immunologic memory established following an early childhood infection. Many questions regarding the timing of imprinting, the impact of the developmental

stage of the immune system, and the effects of maternal antibody at the time of an initial infection remain unanswered, as does the impact of imprinting on the early development of T-cell-mediated immune memory. The effect of immunization with either IIV or LAIV before a first infection also remains undefined, as much of the data on imprinting are in adult cohorts first exposed to influenza via a natural infection. With universal influenza immunization, more

children are first being exposed to this virus via inactivated and/or live attenuated vaccinations that establish preexisting immunity and may alter the ability of early infections to bias subsequent immune responses (Fig. 1). Further, a better understanding of the duration of protection that natural influenza infection provides, how this protects against infection with a drifted virus in children, and how the host immune response is subsequently remodeled on repeated

Influenza-naïve infant

- Complex maternal antibody
- Naïve CD4 and CD8 T-cell repertoire
- Developmentally immature immune system
- Circulating maternal Ab could impact immune response to infection

Influenza-naïve toddler

- Naïve influenza-specific CD4, CD8, and B cells
- Little or no preexisting circulating antibody
- Prolonged duration of viral antigen

Infant/toddler post-IIV immunization

- HA-focused CD4 T-cell and B-cell response
- Circulating HA antibody
- Developmental status of the immune system depends on age at time of infection
- Preexisting HA-specific Ab may limit infection/duration of antigen presentation

Toddler post-LAIV immunization

- Diverse memory CD4 and CD8 T-cell responses
- Diverse but limited abundance of B cells and circulating Ab

Postinfection

- Diverse CD4 and CD8 T-cell responses
- Diverse B-cell response and circulating Ab response, including stalk-reactive Ab

Figure 1. Impact of both the developmental stage of an infant's immune system and preexisting influenza-specific memory at the time of a first influenza infection. Different forms of prior antigenic exposure will impact the preexisting B- and T-cell repertoire, with development of influenza-specific immunity postinfection influenced by both the repertoire of available memory cells and the availability of antigen.

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influenza exposures is necessary. Understanding these issues is critical to defining how early immune history shapes lifelong anti-influenza immune memory.

CONCLUSIONS

Children are unique as they are relatively immunologically naive to influenza virus, leading to increased morbidity on infection. Further, the age and developmental status of the immune system on an initial exposure may contribute to unique manifestations of disease and have a substantial impact on the development of immunologic memory following infection or vaccination. Further research will need to more completely evaluate the development of anti-influenza immunity throughout childhood via the application of unbiased approaches to longitudinal cohorts to understand the complex interplay between the route and order of antigenic exposures, the developmental state of the immune system, and the environmental and genetic factors in shaping immunologic memory. Through a better understanding of how immunity develops during this critical window, insights into both early life priming and the complexity of the anti-influenza immune response will be gained, enabling development of longer lasting and more efficacious influenza vaccines that are effective across the human population.

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