EDITORIALS

Baloxavir for Postexposure Prophylaxis against Influenza in Households

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In the United States, antiviral treatment of influenza is recommended as soon as possible in hospitalized patients and in outpatients who are at increased risk for influenza complications or have progressive disease, and it can be considered in non–high-risk patients presenting within 2 days after the onset of illness (early treatment).[1,2] The neuraminidase inhibitors oseltamivir, zanamivir, and peramivir have been approved by the Food and Drug Administration (FDA) for the early treatment of uncomplicated influenza. Oseltamivir is recommended for the treatment of influenza in hospitalized patients.[1] Neuraminidase inhibitors block the influenza viral surface protein neuraminidase to inhibit release of progeny viruses from infected respiratory cells. Baloxavir marboxil (baloxavir) is FDA-approved for the early treatment of uncomplicated influenza in persons 12 years of age and older, including those at risk for complications. After oral administration, baloxavir is converted to the active form of the drug, which inhibits the function of endonuclease within the polymerase acidic protein subunit of influenza viral polymerase. Randomized, controlled trials have shown that the clinical benefit with one dose of baloxavir is similar to that with 5 days of oseltamivir for the early treatment of influenza in non–high-risk and high-risk adolescents and adults.[3,4] Unlike oseltamivir, baloxavir reduces influenza virus levels in the upper respiratory tract as early as 24 hours after a single dose.[3]

Preexposure or postexposure prophylaxis is generally not recommended in most persons or household members but can be considered in persons at very high risk for influenza complications in whom influenza vaccination is expected to have low effectiveness, such as severely immunosuppressed persons.[2] However, to control institutional outbreaks of influenza, a bundle of interventions is recommended, including antiviral treatment in persons with influenza and postexposure prophylaxis in exposed persons.[2] Because the incubation period and serial interval is short, interventions to interrupt the transmission of influenza must be initiated promptly when influenza is suspected or confirmed.

Ikematsu and colleagues now report in the *Journal* the results of a randomized, placebo-controlled trial of baloxavir for postexposure prophylaxis against influenza in Japanese households during the 2018–2019 season.[5] The trial participants were the household contacts of 545 index patients who had received a diagnosis of influenza at primary care clinics. The participants were randomly assigned to receive a single dose of baloxavir or placebo and were followed for 10 days. Nasopharyngeal swabs were collected for influenza testing by means of reverse-transcription–polymerase-chain-reaction (RT-PCR) assay and to identify viruses with reduced susceptibility to baloxavir by sequencing. Serum samples collected at baseline and 2 to 3 weeks later were tested to assess seroconversion. Pregnant women and immunocompromised persons were excluded; baloxavir is not recommended for these groups.[1]

More than three quarters of the 749 participants were adults. In the overall modified intention-to-treat population, which included participants with or without influenza at baseline, the

risk of laboratory-confirmed influenza was significantly lower, by 86%, among those who received baloxavir than among those who received placebo (1.9% [7 of 374] vs. 13.6% [51 of 375]; adjusted risk ratio, 0.14; 95% confidence interval [CI], 0.06 to 0.30; P<0.001). The findings were similar when the analyses were restricted to participants who were negative for influenza by RT-PCR assay at baseline or to persons at high risk for influenza complications. Among children younger than 12 years of age, the risk of RT-PCR–confirmed influenza was 73% lower among those in the baloxavir group than among those in the placebo group (adjusted risk ratio, 0.27; 95% CI, 0.08 to 0.90). Nearly all influenza virus infections in the households were due to influenza A viruses. The percentage of participants who had asymptomatic infections confirmed by RT-PCR assay or seroconversion did not differ meaningfully between the baloxavir group and the placebo group. The incidence of adverse events was similar in the two groups.

The large benefit of postexposure prophylaxis with single-dose baloxavir in reducing the transmission of influenza should be considered in the context of several issues. Among the index patients, 74% were younger than 12 years of age, and all received treatment with antiviral agents (53% received baloxavir) according to standard clinical practice in Japan; 73% of the household contacts received baloxavir or placebo within 24 hours after the onset of illness in their index patient. However, baloxavir is currently not FDA-approved for treatment of influenza in patients younger than 12 years of age or for prophylaxis in persons of any age. Unlike in Japan, where patients typically seek medical care for influenza testing and early antiviral treatment soon after the onset of illness, in the United States, even high-risk patients with influenza may not present within 2 days after the onset of illness or may not always receive early antiviral treatment.[6] Ikematsu and colleagues reported that influenza viruses with polymerase acidic protein I38/T/M or E23K mutations associated with reduced susceptibility to baloxavir were detected in 15 of 374 participants (4%) in the baloxavir group. In 7 participants in the baloxavir group, transmission of influenza viruses with reduced susceptibility to baloxavir from a baloxavir-treated index patient (in 5 participants) or from a nonhousehold close contact (in 2 participants) could not be ruled out. Public health concerns are that viruses with reduced susceptibility to baloxavir can emerge more frequently in baloxavir-treated children and may be associated with prolonged illness, longer viral shedding, and rebound in influenza virus levels in the upper respiratory tract[3,7] and that limited person-to-person transmission can occur.[8] Global surveillance is essential to monitor circulation of influenza viruses with reduced susceptibility to baloxavir.

This trial adds baloxavir to other antiviral agents (i.e., the neuraminidase inhibitors oseltamivir and zanamivir) that have shown efficacy in reducing the transmission of influenza virus in households when used for early treatment in index patients and for postexposure prophylaxis in their contacts.[9,10] Further studies are needed to assess whether administering additional doses of baloxavir for treatment and for postexposure prophylaxis might reduce the emergence and transmission of influenza viruses with reduced susceptibility to baloxavir and whether the combination of baloxavir for early treatment in symptomatic patients and oseltamivir for prompt postexposure prophylaxis in their close contacts might be useful for controlling institutional outbreaks. Finally, clinicians are reminded that the primary prevention of influenza is through annual influenza vaccination.

The views expressed are those of the author and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

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Growth and the Microbiome — Integrating Global Health with Basic Science

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Linear growth failure, or stunting, is a prevalent condition arising from undernutrition that has been identified as a major global health problem.[1] Stunting is strongly associated with economic, health, and neurocognitive sequelae, making linear growth a major nutrition priority. Interventions that have focused on the supplementation of macronutrients and micronutrients[2,3] and targeted efforts to improve water quality, sanitation, and hygiene have shown limited efficacy in combating growth failure.[4]

One potential causative factor that numerous studies have associated with stunting is environmental enteropathy (also called environmental enteric dysfunction [EED]), a subclinical syndrome that was first described in the 1960s. This disorder, which has been observed in persons residing in and traveling to tropical locations, is characterized by intestinal villous blunting and histologic changes that are consistent with intestinal inflammation. Efforts to disentangle and decipher the relationship between stunting and EED have raised a series of critical questions. Does such enteropathy, as currently defined, lead to stunted growth? Do microbes that are resident in the small intestine contribute to the pathogenesis of enteropathy? What are the molecular mechanisms connecting enteropathy to stunted growth?

A study by Chen and colleagues[5] in this issue of the *Journal* presents evidence that the hitherto unexplored duodenal microbiota can induce villous flattening that is associated with childhood stunting, particularly in children who do not have a response to nutritional therapy. This landmark investigation is built on a decade of research probing causal roles of the intestinal microbiota in nutritional phenotypes. Matching the scale of the problem, the methodical process by which this study has been constructed over time is in itself instructive. By connecting clinical field sites to state-of-the-art bench experimentation, the authors provide a molecular definition of EED that in turn yields potential mechanisms and therapeutic targets for the vexing problem of stunting.

Knowledge from mouse models supports a critical role in postnatal development for the gastrointestinal microbiome, where it has a major effect on the maintenance of gut-barrier function, on the innate and adaptive immune systems, and on shaping host metabolism and nutrient processing. To this end, Chen et al., along with members of the International Centre for Diarrhoeal Disease Research, Bangladesh, and other collaborators, sought to describe the trajectory of microbial communities in human populations from distinct backgrounds. In longitudinal studies involving unrelated children with varying nutritional statuses who were raised in Malawi, Bangladesh, and other sites, the authors have identified shared components of the microbiome,[6,7] including postnatal development features among children across geogra-