heart function. The purpose of this study was to examine the cardiac effects of perinatal exposure to antiretroviral therapy.

STUDY POPULATION. This was a prospective multisite cohort study with 2 groups of HIV-uninfected infants of HIV-infected mothers: 136 infants had been exposed to antiretroviral therapy, and 216 were unexposed.

METHODS. Echocardiograms were obtained between birth and 24 months of age. Data were expressed in mean *z* scores.

RESULTS. Mean left ventricular mass *z* scores were consistently lower in girls exposed to antiretroviral therapy than in those not exposed. These differences persisted to the end of study at 2 years. Similar differences were noted for boys but were smaller. Septal wall thickness and left ventricular dimension were smaller than expected in exposed infants, but left ventricular contractility was higher in exposed infants.

CONCLUSIONS. Exposure to antiretroviral therapy is associated with reduced left ventricular mass and size and septal wall thickness. It is also associated with increased left ventricular fractional shortening and contractility up to 2 years of age. Fetal exposure to antiretroviral drugs seems to impair myocardial growth but improves left ventricular function.

REVIEWER COMMENTS. That exposure to potent nucleoside analogs in utero might have a variety of adverse effects is not surprising. The mechanism of reduced cardiac growth in antiretroviral drug–exposed but HIV-uninfected infants is unknown. However, nucleoside analog–associated suppression of mitochondrial DNA replication might be responsible for this effect. That organogenesis is not more severely affected with long-term exposure to such agents is reasonably comforting. However, only long-term follow-up of antiretroviral drug–exposed infants will address this concern.

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An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis

Berry MPR, Graham CM, McNab FW, et al. *Nature*. 2010;466(7309):973–977

PURPOSE OF THE STUDY. Most people infected with *Mycobacterium tuberculosis* (TB) develop a latent form of the disease and remain asymptomatic; however, approximately 10% of these people are at risk of developing active, transmissible disease in their lifetime. An inability to accurately identify these at-risk patients with conventional tests has limited efforts to control TB. The purpose of this study was to identify novel biomarkers of active disease by using genomic techniques.

STUDY POPULATION. The investigators generated genome-wide transcriptional profiles from the blood of patients with active TB (before treatment), patients with latent TB, and healthy controls. This study was conducted at St Mary's Hospital in London, United Kingdom, and the University of Cape Town in South Africa.

METHODS. Whole blood was obtained from healthy volunteers and patients with TB before starting antimicrobial therapy. A subset of patients diagnosed with active TB were also sampled 2 and 12 months after starting therapy. RNA was extracted from the whole blood of these subjects and used in a genome-wide microarray analysis. Extent of disease was assessed by plain chest radiographs.

RESULTS. The authors identified a distinct 393-transcript signature that defined patients with active disease. In addition, this transcript signature strongly correlated with extent of disease in patients with active TB. It is interesting to note that between 10% and 25% of patients with latent TB had similar transcript profiles to those patients with active disease, which suggests that this profile might identify those at risk for developing active disease. After 2 months of therapy, the transcriptional signature in patients with active TB reverted back to that of healthy controls, which suggests that this signature could be used to monitor the course of the disease. Using data-mining strategies, the authors found that the largest set of transcripts that changed in active TB were those induced by type I interferon (IFN) or IFN-γ in cells that were likely of neutrophil and monocyte origin.

CONCLUSIONS. A unique, treatment-sensitive, genome-wide transcriptional signature predominantly in phagocytes is associated with active TB and might predict those patients at risk of developing active disease. Type I IFN might play a larger role in the pathogenesis of TB than was previously appreciated.

REVIEWER COMMENTS. Development of an accurate biomarker for disease progression and treatment response would be a quantum leap forward in the global fight against TB and would potentially be useful for other similar diseases. This study is the first to associate active TB with a specific gene-expression signature that could be used to monitor those patients on therapy and identify those at risk of treatment failure. More research is needed to determine whether this signature could be used as a marker to identify those with latent TB and at risk of going on to develop active disease. This signature could be extremely valuable in aiding the diagnosis and

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treatment of TB, which remains a major cause of morbidity and mortality worldwide.

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Burden of Seasonal Influenza Hospitalization in Children, United States, 2003 to 2008

Dawood FS, Fiore A, Kamimoto L, et al; Emerging Infections Program Network. *J Pediatr.* 2010;157(5): 808–814

PURPOSE OF THE STUDY. To estimate the rates of hospitalization with seasonal influenza in children younger than 18 years from a large, diverse surveillance area during 2003–2008.

STUDY POPULATION. A case-subject was defined as a child younger than 18 years residing in the surveillance area who was hospitalized with laboratory-confirmed influenza virus infection from the 2003–2004 and 2007–2008 influenza seasons. Surveillance was conducted through the Centers for Disease Control and Prevention Emerging Infections Program Network, which included up to 10 different states and 5.3 million children.

METHODS. Hospitalized children were identified retrospectively; clinicians made influenza-testing decisions. Data collected from the hospital record included demographics, medical history, and clinical course. Incidence rates were calculated with census data.

RESULTS. The highest hospitalization rates occurred in children younger than 6 months (seasonal range: 9–30 per 10 000 children), and the lowest rates occurred in children aged 5 to 17 years (0.3–0.8 per 10 000). Overall, 4015 children were hospitalized, 58% of whom were identified with rapid diagnostic tests alone. Forty percent of the children who were hospitalized had underlying medical conditions; asthma (18%), prematurity (15% of children younger than 2 years), and developmental delay (7%) were the most common. Severe outcomes included ICU admission (12%), respiratory failure (5%), bacterial coinfection (2%), and death (0.5%).

CONCLUSIONS. Influenza-associated hospitalization rates varied according to season and age and likely underestimated true rates, because many hospitalized children are not tested for influenza. The proportion of children with severe outcomes was substantial across seasons. Quantifying the incidence of influenza hospitalization and severe outcomes is critical to defining disease burden.

REVIEWER COMMENTS. Children younger than 6 months had the highest rates of hospitalization across all seasons. Because these children cannot receive the influenza vaccine, immunization of household contacts, out-of-home caregivers of children in this age group, and pregnant women and women who are or will become pregnant during influenza season remains the primary way to reduce the risk of influenza in infants younger than 6 months. The data from this investigation should provide an even stronger argument for recommending the influenza vaccine for appropriate patients.

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A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. *N Engl J Med.* 2011;364(2): 116–126

PURPOSE OF THE STUDY. To examine the efficacy of treatment of acute otitis media (AOM) with amoxicillin-clavulanate.

STUDY POPULATION. The study included a total of 319 children aged 6 to 35 months with AOM.

METHODS. The diagnosis of AOM was made with strict criteria, including signs on physical examination and typical symptoms. The subjects were randomly assigned to receive amoxicillin-clavulanate or placebo for 7 days. The primary outcome was the time to treatment failure from the first dose until the end of treatment on visit day 8. Treatment failure was based on the overall condition of the subjects (including adverse events) and otoscopic examination.

RESULTS. Among the subjects who received amoxicillin-clavulanate, treatment failure occurred 18.6% of the time compared with a rate of 44.9% for the subjects who received placebo ($P < .001$). This difference was already apparent at the first scheduled visit at day 3, at which time 13.7% of the subjects who received amoxicillin-clavulanate, compared with 25.3% of subjects who received placebo, had treatment failure. Amoxicillin-clavulanate reduced the progression to treatment failure by 62% ($P < .001$) and the need for rescue treatment by 81% ($P < .001$). Adverse events (primarily diarrhea) were significantly more common in the amoxicillin-clavulanate group than in the placebo group.

CONCLUSIONS. Children with AOM (aged 6–35 months) treated for 7 days with amoxicillin-clavulanate had a much lower rate of treatment failure and much lower need for rescue treatment than children treated with placebo. However, the children treated with amoxicillin-clavulanate had more adverse effects.

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Pediatrics 2011;128;S145
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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