to services with previously documented effectiveness eliminates the opportunity to try new things. Advancing the leading edge of innovation in research, policy, and practice across sectors will require community-based settings that provide the kind of environment in which creativity flourishes. This demands a flexible approach to planning and funding that encourages risk taking, promotes learning from failure, and supports continuous adaptation before an intervention is ready for a randomized trial. Its successful application presents a dramatic contrast to conventional research, which requires strict adherence to a predetermined protocol and fixed period of data collection. The short-cycle nature of the innovation process feeds on continuous sharing of preliminary findings. The academic approach delays dissemination until the publication of peer-reviewed results. The magnitude of this required cultural shift should not be underestimated, but the potential gains are huge and the status quo is untenable.

A brighter future for children whose life prospects are threatened by adversity requires that we build on the seminal contributions of programs like the NFP and leverage advances in 21st-century science to catalyze fresh thinking that changes the narrative for early childhood investment. Improving program quality, enhancing service coordination, and scaling effective interventions are necessary but not sufficient. The marching orders are clear—we must embrace a spirit of constructive dissatisfaction with best practices, continually design and test new ideas, learn from things that do not work, and settle for nothing less than breakthrough impacts on important outcomes.

ARTICLE INFORMATION

Author Affiliation: Center on the Developing Child, Harvard University, Cambridge, Massachusetts.

Corresponding Author: Jack P. Shonkoff, MD, Center on the Developing Child, Harvard University, 50 Church St, Cambridge, MA 02138 (jack_shonkoff@harvard.edu).

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Newborns, One of the Last Therapeutic Orphans to Be Adopted

Justin L. Stiers, MD; Robert M. Ward, MD

Years of limited study of drugs in pediatric patients after 1962 left 75% to 80% of approved drugs lacking adequate pediatric prescribing information according to Shirkey[1] in 1968 and later Wilson[2] in 1999. In November 1997, bipartisan congressional legislation provided a novel solution to this problem. The Food and Drug Administration (FDA) Modernization Act of 1997[3] provided an incentive of a 6-month extension of existing market protection/exclusivity for all products containing the active ingredient being tested in return for successful completion of pediatric studies specified by the FDA in a Written Request. Studies could include both on-label and off-label indications. This reward, designated the carrot, was complemented the next year by the 1998 Pediatric Final Rule, a stick that required study of new drugs in pediatric patients for the indication that was proposed for approval in adults. Although the 1998 regulation was later overturned by Judge Kennedy as an illegal expansion of FDA authority, almost all of its provisions were codified by Congress in 2003 as the Pediatric Research Equity Act.[4] The study of drugs in pediatric patients increased along with new pediatric labeling, propelled by a stick (Pediatric Research Equity Act) and a carrot (the Best Pharmaceuticals for Children Act [BPCA]). These were renewed in 2007 and made permanent in 2012.[5] The success of these legislative experiments to increase pediatric studies of medications has been demonstrated by approval of the 500th pediatric label change in 2013.[6]

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Not all pediatric patients benefited from the success of these legislations to increase the study of drugs in the pediatric population. By November 2002, 5 years after passage of

the FDA Modernization Act, only 7 label changes included neonates and most of these were for human immunodeficiency virus (HIV) treatment.[6] In 2009, a review of ClinicalTrials.gov found that within pediatric studies, only 6% included neonates.[7] Laughon et al[8] provide in this issue of the journal the most comprehensive analysis of the effects of this legislation on the study and labeling of drugs for newborns.

Using a database that included a cohort of 446 335 neonatal intensive care unit (NICU) patients from 290 NICUs throughout the United States, Laughon et al compared the drugs used in the NICU with the drugs that were studied in neonates to obtain exclusivity. Only 28 of 406 drugs (7%) were studied in neonates, but 46% (13) of these 28 drugs were never used in the NICU. Of the remaining 15 drugs, 8 were used in less than 0.013% of patients. For several of these drugs, anesthetics and HIV drugs, the lack of use in the NICU is understandable. Congenital HIV is now rare in the United States largely because of the success of an older drug, zidovudine, so the newer drugs may not be needed in newborns. Clearly, drugs for infants with HIV deserve continued study for the thousands of infants and children around the world who are infected at birth. With respect to current legislation in the United States, the limited use of several drugs that were studied in neonates emphasizes the potential need for other approaches to increase studies in this pediatric population.

Studying drugs in newborns according to the FDA standards of Good Clinical Practice can be a significant challenge. The amount of blood required for measuring safety laboratory values when added to the volume required for pharmacokinetic measurements quickly exceeds safe limits in a 600-g newborn at 26 weeks of gestation with a blood volume of less than 2 oz. Lung function, cardiac function, and even renal function are hard to measure in this population and harder yet to evaluate for efficacy without gold standards for normal. Even though the limited study of drugs in newborns becomes more understandable, it is more concerning that the studies being conducted may not meet the therapeutic needs of this developmentally immature population.

Several drug studies that have led to labeling have contributed significantly to the care of sick newborns and increasing their survivals, such as those for surfactants and inhaled nitric oxide (iNO). The majority of neonatal therapeutics are based on published literature rather than drug labels. It is important to distinguish between a labeled indication for use and clinical effectiveness. For example, iNO is only labeled for use in term and near-term neonates with hypoxic respiratory failure and pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.[9] As Laughon et al point out, iNO was shown to be ineffective in prevention of bronchopulmonary dysplasia.[10] The absence of additional labeled indications for neonates does not deem any use outside of these settings as inappropriate. Many neonatologists have treated premature neonates younger than 36 weeks' gestation with iNO and improved their oxygenation and reduced their signs of pulmonary hypertension. Given the current limitations in labeling of drugs for neonates, the statement by Laughon et al is incorrect that "many neonates are exposed to drugs that are not indicated in this population, exposing them to unnecessary adverse events without the possibility of clinical benefit."[8] This implies that all off-label use results in unnecessary exposure without benefit. Many effective treatments for neonates are published but are not included in the drug label.

The process of labeling of drugs takes many years during which research may reveal new treatments that are not even proposed for the label. Another challenge in labeling for newborns involves the frequent use of quite old medications in neonatal care, long after a drug's market exclusivity has expired. The BPCA law in 2002 included a process to label off-patent drugs for neonates based on new data developed through collaboration between the National Institutes of Health and FDA. This BPCA effort uncovered many unexpected regulatory challenges. Not all drugs remained off-patent. Studies had to be designed and completed to comply with the high standards of Good Clinical Practice. Finally after successful completion of studies, the label had to be changed. The owner of the label, the original innovator company, may no longer be in business or continue to make the drug. The pediatric leaders at the National Institutes of Health and FDA have persevered to address these issues, and the first drugs are now going through a new docket procedure to gain a pediatric label.[11]

Completion of studies on which to base a label for newborns, especially the most vulnerable extremely premature newborns, presents significant challenges. This study by Laughon and colleagues shows that the current process often does not address their therapeutic needs. As the last laws requiring pediatric studies of new drugs and incentivizing studies through BPCA became permanent, the law also requires neonatal expertise be included at the FDA for the next 5 years. This is unlikely to be long enough to address the therapeutic needs of newborns. History has shown that a stimulus is necessary to increase pediatric studies. Completion of studies in neonates may require a greater stimulus, but it is unacceptable to leave our most vulnerable pediatric population outside the safety net of evidence-based studies to remain therapeutic orphans.

ARTICLE INFORMATION

Author Affiliations: Division of Neonatology, University of Utah, Salt Lake City.

Corresponding Author: Robert M. Ward, MD, Division of Neonatology, University of Utah, 295 Chipeta Way, Salt Lake City, UT 84108 (robert.ward@hsc.utah.edu).

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The Beginning of the End of Measles and Rubella

Mark Grabowsky, MD, MPH

Measles was first imported into the New World in the early 16th century by European colonists, often with devastating effects on native populations. Rubella importation followed and led to congenital rubella syndrome. It is estimated that during the following 5 centuries, more than 200 million people globally died of measles. Disease incidence fell rapidly after the availability of vaccines in the United States for measles in 1963 and rubella in 1969, and after the availability of a combined measles-rubella vaccine in 1971. As vaccination expanded into other countries of the Americas, the Pan American Health Organization established a goal to eliminate measles from the Western hemisphere by 2002 and rubella by 2010. By 2004, transmission had been interrupted in the United States. However, there has been concern that pockets of transmission persisted or that transmission could be reestablished if immunization coverage levels declined.

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In this issue of the journal, Papania and colleagues[1] report that an expert panel convened by the Centers for Disease Control and Prevention has determined that the elimination of endemic measles, rubella, and congenital rubella syndrome has been sustained for a decade. Along with certifications from other countries in the Americas, the entire Western hemisphere will be certified free of indigenous transmission.

The elimination of measles and rubella from the Western hemisphere is a triumph of public health with several important implications. First, imported cases of measles and rubella will still likely occur as long as there remain endemic areas in the world. That these imported cases do not result in sustained transmission is confirmation that the level of population immunity is high enough for elimination. Prior to 1990, Mexico was the leading source of measles importations into the United States, but this year, half of all importations into the United States were from Europe.[2] Since 2008, there has been a resurgence of measles cases in Western European countries. The majority of these outbreaks have been in unimmunized populations in countries where national immunization programs are being challenged by a combination of public and political complacency regarding the value of immunization and by the rising influence of antivaccination groups. After 500 years, we have now returned to a situation where the Americas are free from indigenous measles and rubella with Europe once again a source of importations.

A second implication of the elimination of measles and rubella in the Western hemisphere is that it is a vindication of US vaccination strategy. Over the years, the United States experienced several false starts for measles and rubella elimination, with multiple missed target dates, but systematically incorporated the lessons learned from each failure into subsequent efforts.[3] The essential elements of the final successful strategy were that (1) coverage with a first dose of measles-mumps-rubella (MMR) vaccine must be early, high, and sustained (in the United States, MMR vaccination rates among children younger than 2 years of age have been more than 90% for a decade); (2) each person must receive 2 doses of MMR vaccine (94.8% of children entering kindergarten have received 2 doses of MMR vaccine[4]); and (3) disease surveillance must include laboratory confirmation of suspected cases (there is a robust surveillance system for measles and genetic analysis of each virus to identify imported cases and their geographic source). It is encouraging that the European region has now endorsed these essential strategies, emphasizing routine vaccination and disease surveillance.[5]

The greatest threat to the US vaccination program may now come from parents' hesitancy to vaccinate their children.[6] Although this so-called vaccine hesitancy has not become as widespread in the United States as it appears to have become in Europe, it is increasing. Many measles outbreaks can be traced to people refusing to be vaccinated; a recent large measles outbreak was attributable to a church advocating the refusal of measles vaccination.[7] Even greater risk may come from parents who delay vaccinations rather than refusing them outright because a delayed vaccination may add more person-years of susceptibility than that due to refusing vaccination. The single most important factor influencing decision making on childhood vaccination is the clear recommendation of a physician—clinicians must recognize their responsibility in supporting early vaccination. To address this issue, the National Vaccine Advisory Committee has convened a working group on vaccine hesitancy and has made some recommendations on how best to respond to it.