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Seven great achievements in pediatric research in the past 40 y

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INTRODUCTION

"We live in extraordinary times...thanks to medical and scientific advances that even a generation ago would have sounded like science fiction…An American born today has a projected average lifespan 20 full years longer than one born in 1925."

–Time Magazine, 12 February 2015

Over the last 40 y there have been dramatic decreases in global mortality and improvements in quality of life. The pace and scope of research progress has been incredible with its roots in basic science and epidemiologic discoveries leading to efficacy and effectiveness trials. Changes in clinical and public health practice and policy have improved health of populations originating from research discovery.

Despite the evident successes, there are current threats to continuing the investment necessary to support critical research. Although the importance of biomedical research was unquestioned for decades, this has changed in the recent times. Historically, the United States has been the global leader in spending on medical research; however, funding has flattened. As an example although the compound annual growth rate for research was >6% from 1994 to 2004, in the last decade this growth has been <1% and in the most recent years has actually declined (1). In addition, Gitterman *et al.* have noted that the National Institutes of Health investment in pediatric research has been flat even during the growth years (2). These funding trends threaten continued progress.

This article highlights seven great achievements in pediatric research of the last 40 y (**Table 1**). Because of research in these areas, children are healthier and safer today and will become healthier adults. As part of a strategic planning effort in 2013, the American Academy of Pediatrics (AAP) Committee on Pediatric Research conducted an open-ended survey of the board members of pediatric professional organizations on the greatest successes in pediatric research and future opportunities. Although there were many achievements to consider, seven achievements were selected (**Table 1**) demonstrating how pediatric research investment has paid off in extending and saving lives. The Pediatric Policy Council, which comprised representatives from the Academic Pediatric Association, the American Pediatric Society, the Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research has been involved in disseminating information on these achievements.

Preventing Disease with Life-Saving Immunizations

One of the most significant advances in child health over the past century has been the use of immunization to prevent disease. Numerous vaccines have saved millions of lives. In the past 40 y, two vaccines have had particularly dramatic effects on morbidity and mortality: *Hemophilus Influenzae* type b (HIB) and rotavirus vaccines.

HIB is a bacterium known to cause invasive disease predominantly in children under 5 y of age, including meningitis, pneumonia, epiglottitis, septic arthritis, and bacteremia. Prior to widespread use of the HIB vaccine, 20,000 children in the United States were infected with HIB each year and 1,200 died annually from the disease (3). HIB was the leading cause of bacterial meningitis in children under 5 y with an estimated 12,000 cases annually (4,5).

Research into the immunogenicity of HIB demonstrated increased antigenic properties and a more robust antibody response to its purified capsular polysaccharide, polyribosylribitol phosphate, when conjugated to a protein carrier (4). Placebo-controlled trials of the effectiveness of the immunologic response to the conjugated HIB vaccine in children showed nearly 100% protection of those vaccinated. This led to the Food and Drug Administration (FDA) approval of the first HIB vaccines for a primary immunization series beginning at 2 mo of age (4). Pediatric clinicians translated research discoveries to practice. Since universal HIB vaccination recommendations in 1991, invasive HIB-associated infections have decreased by 99% in the United States (3).

Rotavirus vaccine was a similar success story. Rotavirus infection is the leading cause of severe pediatric diarrheal illness and dehydration worldwide with 450,000 deaths of children under 5 y of age in 2008 (6). Prior to the development of a vaccine, 20–70

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deaths in the United States each year were attributed to rotavirus infection (7–9). In the 1970s, researchers noted the protective effects of prior rotavirus infection against future illness. Building upon this, initial trials used a live attenuated monovalent animal-strain vaccine administered orally (7). Following decades of safety and efficacy testing, this first rotavirus vaccine was licensed in 2006 and approved by the FDA (10) for routine immunization of infants in a three-dose series beginning at 2 mo of age. This was followed by the licensing of an oral live attenuated two-dose rotavirus vaccine in 2008 (7,11,12). A randomized, double-blind, placebo-controlled trial showed vaccination to be 87% effective against rotavirus gastroenteritis in general, and 96% effective against severe gastroenteritis (10,13,14). In the United States, routine vaccination with rotavirus vaccine is estimated to prevent 40,000–60,000 hospitalizations each year (14–16). The effect is more significant among poorer nations, where rotavirus vaccination in 72 countries receiving aid from the international Gavi vaccine alliance is expected to save 2.46 million child deaths between the years of 2011 and 2030 (17).

Vaccines for HIB and rotavirus have significantly decreased morbidity and mortality in children worldwide. Research into the development of new vaccines continues to be important for old and emerging infectious diseases.

Table 1. Seven great achievements in pediatric research in the past 40 y

Achievements
• Preventing disease with life-saving immunizations
• Reducing sudden infant death with back to sleep
• Curing a common childhood cancer
• Saving premature babies by helping them breathe
• Preventing HIV transmission from mother to baby
• Increasing life expectancy for children with chronic diseases
• Saving lives with car seats and seat belts

Reducing Sudden Infant Death with Back to Sleep

Sudden Infant Death Syndrome (SIDS), or "crib death", is defined as the sudden death of an infant <1 y of age that remains unexplained despite an autopsy, review of the clinical history, and examination of the death scene (18). SIDS is the leading cause of death in United States infants aged 1 mo to 1 y (19,20). In 1993, nearly 4,700 US infants died of SIDS (21).

Case–control studies conducted in the United Kingdom, Ireland, Australia, Hong Kong, and the United States found that prone sleep position was associated with SIDS (22). The National Institute of Child Health and Human Development (NICHD) convened meetings of researchers, practitioners, government agencies, and parents in 1992 and 1994 to analyze the data from around the world and make policy recommendations (19). In 1992, the AAP Task Force on Infant Positioning and SIDS published a policy, recommending infants be placed on their back or side to sleep (22). By 1994, it was widely accepted that supine sleep position was safest (19) and the Back to Sleep campaign was initiated by the NICHD, AAP, Maternal and Child Health Bureau of the Health Resources and Services Administration, SIDS Alliance (now known as First Candle), and the Association of SIDS and Infant Mortality Programs (23,24).

The Back to Sleep campaign resulted in a dramatic increase in supine sleep position from 13% in 1992 to 76% in 2006 (18). Figure 1 shows that during the same period, the US SIDS rate dropped by ~50% (18) echoing similar results documented around the world (19). In 2010, the number of US SIDS deaths was 2,063 (25).

The Back to Sleep campaign recently celebrated its 20th anniversary and is an incredible success story. However, challenges remain, pointing the way to future research avenues. One major challenge is the persistent racial disparity in the incidence of SIDS, with higher rates for African American and Native American infants (18,23). Although the prevalence of supine sleeping increased rapidly after 1994, it has plateaued during the past decade (18). As ongoing research

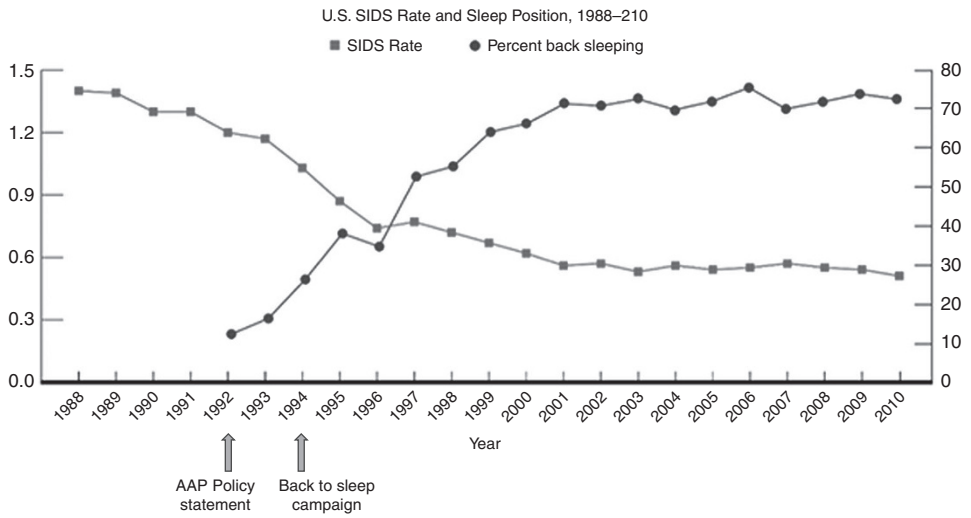

Figure 1. Sudden Infant Death Syndrome (SIDS) Rate and Back Sleeping, U.S., 1988–2010 (Deaths per 1,000 Live Births). SIDS Rates Source: Centers for Disease Control and Prevention, National Center for Health Statistics; Sleep Position Data: National Institute of Child Health and Human Development (NICHD), National Infant Sleep Position Study.

has demonstrated other risk and protective factors for SIDS and other causes of sleep-related infant deaths highlighted in the AAP Task Force on SIDS policy statements of 2005 (23) and 2011 (18), focus has broadened beyond advocating supine sleep position. Recognizing the new data and public health needs, the Back to Sleep educational and outreach effort has transformed into the Safe to Sleep campaign (24).

Curing a Common Childhood Cancer

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and important lessons can be learned from the successful evolution of childhood ALL therapy. Although prior to 1950, the diagnosis of childhood leukemia was uniformly fatal and in the 1960s survival was only 15–20%, survival rates for childhood ALL have now reached 90% (26). **Figure 2** shows the dramatic decline in mortality rates for ALL and other pediatric cancers. This remarkable turnabout came from the development of highly disciplined clinical trials investigating the use of combination chemotherapy and the recognition of the critical importance of presymptomatic central nervous system-directed therapy (27). Over the past 20 y the benefit of treatment intensification has been recognized, cranial irradiation has been replaced by intrathecal chemotherapy in most children, and risk-stratified treatment protocols have been adopted (28).

In recent years, comprehensive genomic analyses have provided important insight into underlying disease biology and have been pivotal in defining novel subtypes and advancing personalized ALL therapy. The identification and successful treatment of the subset of children with Philadelphia chromosome-positive (Ph+) ALL with a combination of a tyrosine kinase inhibitor and chemotherapy has served as a treatment paradigm (29).

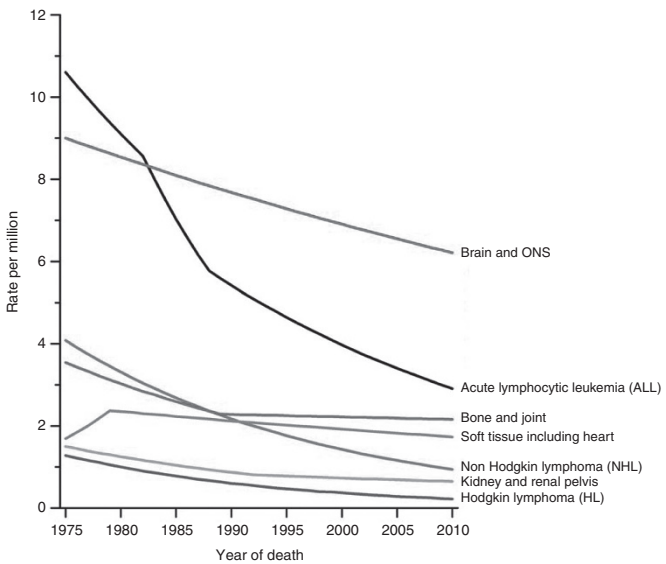

Figure 2. Trends in pediatric cancer mortality rates by site, aged from birth to 19 y, U.S., 1975–2010. ONS, other nervous system. Note: Lines represent joinpoint fitted trends. The average annual percent change for cancers with significant trends during the most recent period: acute lymphocytic leukemia (–3.1* during 1988–2010), brain (–1.1* during 1975–2010), non-Hodgkin lymphoma (–4.1* during 1975–2010), soft tissue (–1.0* during 1979–2010), kidney (–1.2* during 1992–2010), and Hodgkin lymphoma (–4.9* during 1975–2010). Source: National Center for Health Statistics, Centers for Disease Control and Prevention. Reproduced with permission from a figure in ref. (95).

Ph-like ALL (10–15% of all childhood B-lineage ALL diagnoses) is a newly defined subset, characterized by a gene expression signature similar to Ph+ ALL, yet lacking the BCR-ABL1 fusion protein, and poor outcomes (30,31). Preclinical studies have demonstrated that tyrosine kinase inhibitor therapy, following the successful paradigm in Ph+ ALL, may be effective for Ph-like ALL as well (32). The success of treating Ph+ ALL with tyrosine kinase inhibitor therapy in combination with chemotherapy has resulted in the need for far fewer children to undergo hematopoietic stem cell transplantation and the same strategy may apply to novel subsets of ALL in the future.

Another exciting area of development in childhood ALL has been in new immunotherapeutics, including bispecific antibodies and engineered T-cell therapy (33). Historically, relapsed ALL has had a dismal prognosis and this remains a leading cause of childhood cancer mortality. After an initial report of the successful treatment of two children with chimeric antigen receptor-modified T-cell therapy targeting CD19 (34), outcomes in additional patients with longer follow-up were reported and complete remission rates of 90% were observed (35). Clinical trials are presently underway.

Ongoing research efforts in childhood ALL include identifying and improving outcomes for the highest risk subsets of ALL patients, including those with recurrent and refractory disease; preventing therapy-related toxicities and improving the quality of life for long-term survivors.

Saving Premature Babies

Prematurity is the leading cause of infant mortality, accounting for over 35% of infant deaths (36). Respiratory distress syndrome (RDS) occurs shortly after birth in most premature infants and it is nearly universal at <28 wk gestation. Untreated, poor lung compliance, atelectasis, and high fatality rates characterize RDS. Discovery of the cause of RDS (surfactant deficiency), characterizing the nature of pulmonary surfactant, and developing and testing surfactant preparations was the result of decades of research.

Physiologist John Clements recognized that the uncountered forces of surface tension would lead to alveolar collapse (37–39). After developing special tools to measure surface

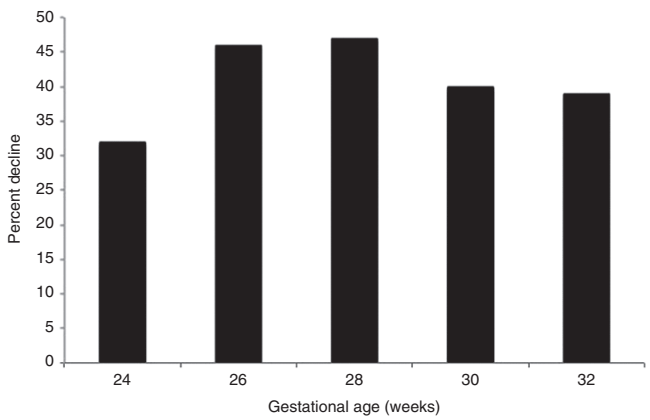

Figure 3. Estimated decline in mortality by gestational age, U.S., between 1985–1988 (before surfactant) and 1995–2000 (after surfactant). Source: Reprinted from ref. (54).

tension, he identified pulmonary surfactant (first called the "anti- atelectasis factor") (40). Avery and Mead made the seminal discovery that surfactant was absent from the lungs of infants who died from RDS, but present in infants who died without pulmonary disease (41).

Investigations then centered on identifying the cells that synthesize and secrete pulmonary surfactant (42–44), and on characterizing its complex composition (45–47). Animal trials followed (48–50) with Fujiwara successfully treating premature infants with RDS using surfactant prepared from cow lungs (51). Large scale randomized double blind placebo-controlled clinical trials were carried out using a synthetic surfactant and a cow lung extracted surfactant. Both preparations reduced the mortality for RDS by >50% (52,53) resulting in rapid FDA approval in 1990–91. Virtually all neonatal intensive care units across the United States and the developed world quickly adopted surfactant for the treatment of RDS, and death rates for premature infants fell precipitously. For infants born between 24 and 32 wk gestation, mortality has dropped by 30–45% after the widespread use of surfactant (54) (**Figure 3**). The change in the field of neonatology has been dramatic; neonatologists who have been practicing for more than 25 y divide their careers into eras of "before surfactant" and "after surfactant" (EA Liechty, personal communication, 2015)

Preventing Human Immunodeficiency Virus Transmission from Mother to Baby

Perinatal transmission of Human Immunodeficiency Virus (HIV) in the United States rose rapidly during the 1980s, reaching a peak in 1991 at an estimated 1,650 HIV-infected infants per y (55). An estimated 15–30% of HIV-infected mothers transmitted the virus to their infants in-utero or intrapartum (56,57).

In 1994, the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group published a landmark clinical trial that demonstrated a 67% reduced risk of transmission of HIV when treating both mothers and infants with zidovudine (58). In 1995, the Centers for Disease Control and Prevention and the AAP released recommendations for universal HIV testing for all pregnant women (59,60). Subsequent studies confirmed zidovudine's efficacy in preventing vertical transmission, especially in combination with other antiretroviral medications.

Widespread use of antiretroviral therapy, universal HIV testing for pregnant women, avoidance of breastfeeding, and scheduled cesarean delivery in mothers at high risk of transmission have decreased the risk of transmission from mother to infant to <2% in developed countries (61). In 2013, there were 93 cases of perinatally acquired HIV in the United States (62), a 94% decrease from the peak in 1991 despite a significant increase in the total number of births (**Figure 4**) (63).

Despite significant progress, however, access barriers to appropriate prenatal care and testing for pregnant women continue to hinder further progress in reducing perinatal transmission of HIV. Recent data show that among mothers of HIV-infected infants, 38% had no prenatal care, 27% were diagnosed with HIV after delivery, and only 29% received antiretroviral medications during pregnancy (64). Improved education and access to care will be vital in the campaign to eliminate the perinatal transmission of HIV.

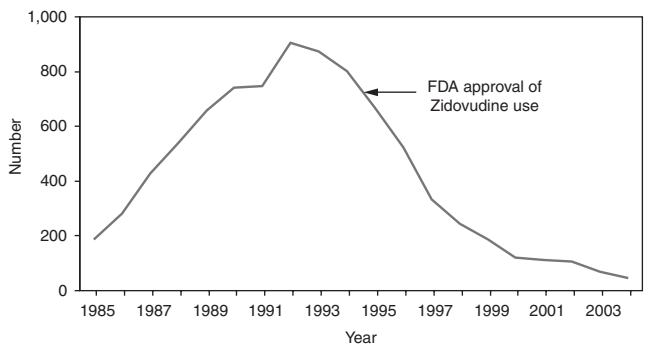

Figure 4. Estimated number of cases of perinatally acquired AIDS*, by year of diagnosis – U.S., 1985–2004. *Acquired immunodeficiency syndrome.
Source: Adapted from ref. (63). Data adjusted for reporting delays and for estimated proportional redistribution of cases in persons reported without an identified risk factor.

Increasing Life Expectancy for Children with Chronic Diseases

Research has advanced the diagnosis and treatment of children with chronic disease. Advances for the two most common life-shortening genetic disorders affecting US children are highlighted here: cystic fibrosis (CF) and sickle cell disease (SCD). Although neither CF nor SCD is yet curable, research has improved life expectancy and quality of life.

Nearly 2,500 American children are born with CF annually; ~30,000 Americans are living with CF (65). In 1989, the CF transmembrane conductance regulator gene was discovered to be the cause of the disease (66). Today ~130 pathogenic mutations known to affect multiple organ systems including the lungs, pancreas, liver, intestines, and reproductive organs have been

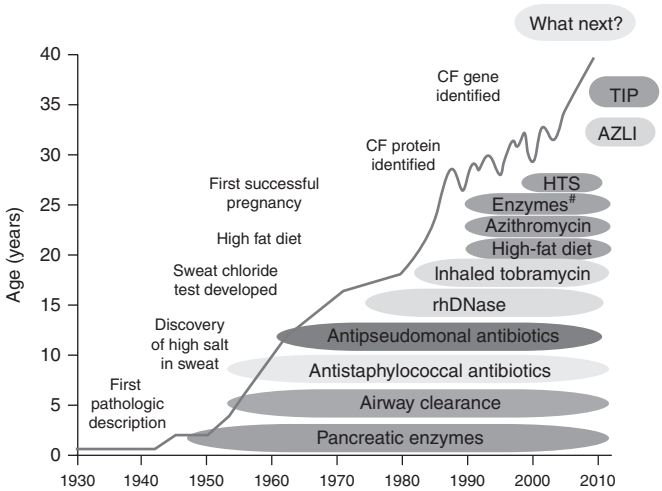

Figure 5. Increases in life expectancy in patients with Cystic Fibrosis (CF), U.S., 1930–2010. Reprinted from ref. (70). CF, cystic fibrosis; HTS, high-throughput screening; AZLI, aztreonam for inhalation solution; TIP, tobramycin inhalation solution; #, enteric-coated pancreatic enzymes. Reproduced with permission of the European Respiratory Society ©: *The European Lung White Book Respiratory Health and Disease in Europe, 2nd Ed.* ©2013 European Respiratory Society, Sheffield, UK. Print ISBN: 978-1-84984-042-2, Online ISBN: 978-1-84984-043-9

identified (67). In CF, recurrent pulmonary infections cause progressive damage leading to progressive obstructive pulmonary disease.

Forty years ago, the median life expectancy was < 25 y (68). Since then research has led to significant advances, including the addition of CF to the US newborn screening panels and the emergence of effective medications, breathing treatments, aggressive nutritional supplementation, research networks (including the CF Foundation Therapeutic Development Network) and multidisciplinary treatment teams. **Figure 5** shows that the combination of medical and social advances have greatly improved the quality of life in children with CF, with life expectancy now above 40 y (69,70).

SCD affects ~100,000 Americans (71). In SCD, clots prevent normal blood flow, resulting in pain crises, infections, and end-organ damage including stroke. Although it had been known since the 1940s that the disease was recessively inherited, and the SCD-causing hemoglobin gene mutation was characterized in the 1950s, more recent discoveries have resulted in novel and effective therapeutic approaches.

Forty years ago, the life expectancy for Sickle Cell Disease was 14 y (72). Like CF, SCD is now part of all US newborn screening programs. Research has led to widespread use of the life-saving medication, hydroxyurea, which increases fetal hemoglobin and reduces red cell sickling and fragility. Recognizing susceptibility to infection, standard of care for SCD incorporates prophylactic antibiotics and vaccines. Bone marrow transplantation has been used as a curative therapy, and gentler and effective means of transplantation are being developed. Policy efforts to increase care access, such as the Children's Health Insurance Program, have increased the reach of medical best practices. Combining preventive care with standardized medical management of sickle cell crises have helped to increase the current life expectancy to more than 40 y of age (73) (**Figure 6**).

Saving Lives with Car Seats and Seat Belts

Motor vehicle injuries remain the leading cause of death for children aged 1–17 (refs. 74,75). Over the past four decades, however, significant headway has been made in reducing pediatric fatality rates due to motor vehicle injuries, dropping by 55–78%, even though the annual number of miles that Americans travel on our nation's highway has doubled over the same period (76–78) (**Figure 7**).

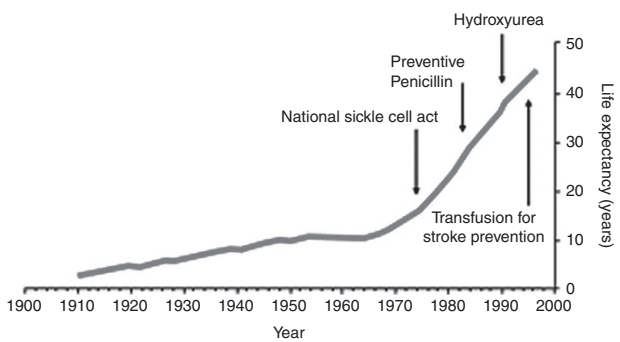

Figure 6. Increases in life expectancy in patients with Sickle Cell Disease, U.S., 1910–2000. Source: National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD.

Researchers discovered that car seats and seat belts could reduce passenger ejections during crashes and save lives. Appropriate car seat use reduces the risk of death for infants by 71% and for toddlers by 54% (75). Appropriate booster seat use for children aged 4–8, when compared with seat belt use alone, can reduce the risk of serious injury by 45% (78). For teenage passengers becoming drivers, graduated driver licensing now in all states are associated with reductions of 38 and 40% in fatal and injury crashes, respectively, among 16-y-old drivers (79).

Reviews find that child safety seat laws themselves decrease death by 35% and increase child safety seat use by 13%, while child safety seat distribution and education programs increase child safety seat possession by 51% and child safety seat use by 23% (80). Still more child motor vehicle deaths could be prevented if effective interventions were increased. Current research is identifying barriers to pediatric passenger safety (e.g., lack of access to car seats, need for education on proper installation or use) (81–84). Important areas for continued research are pediatric subgroups who are at higher risk for death from motor vehicle injuries: children 4–8 y of age, teens, children from low-income backgrounds, and those living in rural settings (85–90).

DISCUSSION

This article highlights seven pediatric achievements, demonstrating how pediatric research has changed the way we raise and care for children, both in medical practice and in everyday life. These successes have involved all four phases of translational research including (T1) basic science discovery, (T2) clinical or population efficacy, (T3) effectiveness trials, and (T4) implementation and dissemination and health services

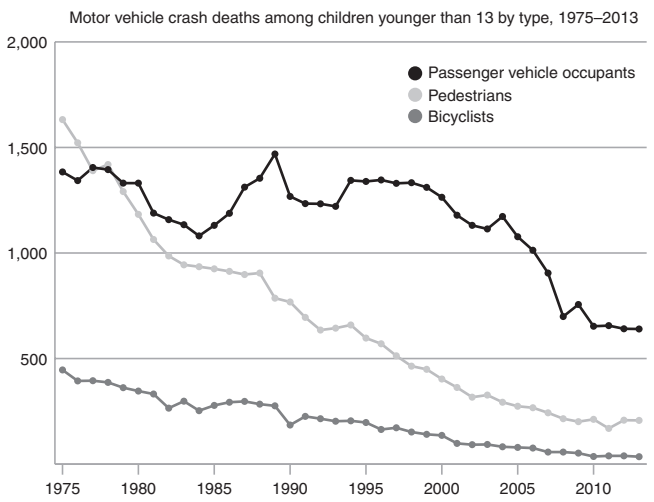

Figure 7. Passenger vehicle child occupant deaths per million children by age, U.S., 1975–2013. Reproduced with permission of the Insurance Institute of Highway Safety, http://www.iihs.org/iihs/topics/t/child-safety/fatalityfacts/child-safety/2013. Source: US Department of Transportation National Highway Traffic Safety Administration Fatality Analysis Reporting System. http://www.iihs.org/iihs/topics/t/child-safety/fatalityfacts/child-safety/2013.

and policy research to improve individual and population health (91,92). Multidisciplinary researchers, pediatric clinicians, staff, and policymakers have all have had important roles in these tremendous achievements.

Isaacs and Schroeder studied lessons learned from public health advances and found that research was one of the common success factors along with advocacy efforts, work with the media, law and regulation (93). Research combined with the other factors have led research translation to practice, policy, and improved health. However, today we often take for granted these research achievements. The AAP has developed a campaign highlighting these pediatric research success stories including a congressional briefing held last year. Video and other materials can be found at the AAP website (94). Pediatric professionals should take pride in these success stories and communicate the importance of research to the public and to policymakers. For example, when a federal research grant is awarded or important discoveries are made, researchers should communicate this to Congressional representatives and the public. Continued research and research funding are essential to maintain past achievements and to ensure future achievements. Communicating research discovery to the public and policymakers is a critical component of implementation, dissemination, and progress.

Though life expectancy has increased, threats to child health in the United States have led some to predict that today's children may be the first generation that does not live longer than their parents (95). Growing research demonstrates that children's health is the foundation for adult health and there is a need to invest early in the life course. We are on the cusp of research discoveries that promise to both prevent disease and find cures. With rapid changes in the health care delivery system, health services research is also a key. Past research's successes have led the way to improved health and development. Continued research is essential to address old and new health challenges and to maintain and advance child health.

AUTHOR CONTRIBUTIONS

T.L.C. conceptualized and drafted the manuscript. N.M., L.D., B.S., A.T.C., E.R., E.S.P., and S.C.D. drafted sections of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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