The *Lancet Child & Adolescent Health* Commission on the future of neonatology

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Neonatal mortality remains unacceptably high throughout the world. Survival of sick infants in their first month of life has improved over the past six decades. However, many comorbidities persist, with lifelong implications for health. The current ecosystem for research and development of drugs and medical devices to treat neonatal disorders is hindering further improvements to neonatal outcomes, especially infants born preterm or needing critical care. Innovation is lagging, and this is a public health problem characterised by multifactorial challenges in leadership, collaboration, regulation, funding, and commercial viability. The *Lancet Child & Adolescent Health* Commission on the future of neonatology was created to consider these challenges and design a roadmap of strategies to accelerate research and development that will innovate and improve health care for neonates. We call for regulatory agencies, governments, funders, industry partners, and clinical researchers from diverse medical fields to invest in effective pathways for drug and medical device development and to unite in responsive and dynamic collaborations with diverse patients, families, and advocacy groups whose engagement in clinical research and advocacy can help neonatologists to achieve the best science and health equity for neonates worldwide, now and in the future.

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Introduction

Neonatology needs innovation through research and development

Optimisation of the health of every newborn infant should be considered a cornerstone of efforts to improve global population health; indeed, in dedicating World Health Day 2025 to maternal and newborn health, WHO recognises newborn health as a critical global issue.[1,2] Increased survival of newborn children in their first month of life, especially those born extremely premature and those with life-threatening disease, reflects progress in perinatal and neonatal medicine in the past 25 years.

Neonatology is a relatively young medical speciality that has contributed scientific advances and clinical developments and generally improved outcomes for sick neonates. Yet neonatal mortality remains unacceptably high throughout the world,[3] and some of the most common health concerns affecting neonates are still very challenging to treat. Off-label or off-licence use of drugs with little evidence of efficacy is very common,[4,5] and the willingness to use these drugs is hampering the development of interventional studies and patient accrual to such clinical trials. Clinical care remains largely supportive, non-specific to the disorder or disease, and based on clinicians' experience rather than high-level clinical evidence. Relatively little research to advance neonatology is taking place, and, of this research, most is occurring in high-resource settings. On a global scale, neonatology is lagging behind other medical specialties in terms of clinical advances to provide adequate and robust preventive care, diagnostics, and therapeutic interventions for common disorders, and in terms of the pace of obtaining and translating scientific knowledge to improve clinical care (panel 1). These challenges in neonatology and the inability to advance health outcomes for newborn children in their first month of life amount to a public health problem that demands the attention of ethics committees, regulatory bodies, health-care providers, industry, governments, and the public. The *Lancet Child & Adolescent Health* Commission on the future of neonatology was created to consider these challenges and take steps to address them.

The catalyst for the Commission was the unexpected decision by a pharmaceutical company to halt an international, multicentre, phase 2b trial of recombinant human IGF1 for preventing bronchopulmonary dysplasia—one of the most common adverse consequences of prematurity—in extremely preterm neonates (NCT03253263). Recombinant human IGF1[6] was one of very few new neonatal medicines to reach later phase evaluation, with no safety or efficacy concerns emerging from the initial phase 2a trial of IGF1 to prevent retinopathy of prematurity in extremely premature infants (NCT01096784).[7] The decision to halt the continuation of the phase 2b trial did a disservice to the many families who consented to participate in a trial they believed would benefit infants globally. Although the trial has restarted with new industry support, we lack confidence in its future.

As a global community of neonatologists, we are concerned that the dearth of innovative research and development is failing to meet the needs and expectations of parents, clinicians, and society. Research and development are essential for the continued evolution of neonatology as a medical specialty and to improve outcomes for neonates. The Commission united a diverse range of stakeholders of newborn health—neonatologists, public health doctors, paediatricians, paediatric surgeons, maternal and fetal medicine

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***Panel 1:* Examples of past advances and current challenges in neonatology**

Major advances in neonatology to date

Advances specific to neonatology

- Continuous positive airway pressure
- Inhaled nitric oxide
- Prenatal steroids
- Surfactant

Advances derived from adult medicine

- Continuous renal replacement therapy
- Extracorporeal membrane oxygenation
- Mechanical ventilation
- Parenteral nutrition
- Therapeutic hypothermia
- Vascular access
- Vital monitoring

Neonatal disorders awaiting sufficiently efficacious diagnostic, preventive, or therapeutic tools

- Allo-immunisations
- Bronchopulmonary dysplasia
- Congenital diaphragmatic hernia
- Intraventricular haemorrhage
- Necrotising enterocolitis
- Periventricular leukomalacia
- Retinopathy of prematurity
- Severe congenital malformations
- Severe metabolic disorders (refers to most, but not all, metabolic disorders, because some might benefit from experimental therapies)

Situations with significant uncertainties

- Growth restriction
- Heart failure
- Hypoxic-ischaemic encephalopathy
- Late and sustained persistent pulmonary hypertension of the neonate
- Liver failure
- Multi-organ failure
- Neonatal acute respiratory distress syndrome
- Phototherapy for extremely preterm infants
- Sepsis
- Septic shock

specialists, nurses, developmental biologists, clinical pharmacologists, technologists, and representatives of regulatory bodies, patient and parent groups, and WHO—around the shared belief that bringing innovation to neonatology requires multifactorial action and is critical for future generations of neonates and for the health and economic prosperity of the general population.

Our work was launched by the EU Commissioner on Healthcare and Food Safety at the 2022 annual congress of the European Association of Perinatal Medicine. We had four core aims: to highlight barriers and challenges that prevent a culture of research and development from flourishing in neonatology; to emphasise the need for a strong scientific knowledge base to improve neonatal medicine; to make the case for greater financial and cultural investment in neonatal research and development; and to provide clear, practical recommendations that facilitate innovation in neonatology and ensure that the opportunities to develop medicines and medical devices for critically ill neonates are seized.

This is a call to action for industries, governments, universities, and academic medical centres, and regulatory authorities, as well as clinicians, researchers, former patients, and families. We propose mission-oriented solutions to tackle obstacles and foster innovation in neonatology across high-income, middle-income, and low-income settings. Our vision for neonatology is a specialty that delivers equitable, improved health care for all neonates worldwide founded on a strong scientific knowledge base created by high-quality medical research (figure 1). The three pillars of equitable health care for neonates are: (1) innovation for both drugs and medical devices; (2) resources, including financial, human, and technical assets; and (3) partnerships between neonatologists and specialists across paediatrics and adult medicine, allied health-care professionals, and families. Details of the Commissioners and our methodology are provided in panel 2.

The cost of inaction

Neonatology cares for the youngest and smallest patients, often in immediate life-threatening situations that require critical care. Patients are growing and physiologically maturing through developmental processes that are extremely sensitive to disease. The underlying genetics, genomics, molecular biology, developmental physiology, and pathophysiologies of the diseases that affect newborn infants each represent a potential therapeutic target. Yet our understanding of these processes remains poor, highlighting the importance of extending research in basic and applied developmental biology.

Research literature specific to the field of neonatology first began appearing in PubMed in the 1950s (appendix p 10). Important advances in the 1980s and 1990s saw the introduction of prenatal steroids, surfactant, and continuous positive airway pressure. Relatively few innovations have been identified and applied since. Furthermore, translation and implementation into clinical practice of new drugs and devices have been slow, possibly as a consequence of small patient numbers for trials.

The history of prenatal steroids is illustrative. Following solid basic science, this low-cost, simple antenatal intervention to enhance lung maturation has significantly improved respiratory and non-respiratory outcomes of preterm infants. But the introduction of prenatal steroid prophylaxis was very slow. Despite steroids being readily available and unpatented (and therefore not needing

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industry support), it took more than two decades following the original research by Liggins and Howie[9] that suggested a benefit before the practice of prenatal steroid prophylaxis was widely accepted. This delay caused the unnecessary loss of lives, begging the question: had funding for research and implementation been available, would antenatal steroid implementation have been quicker? To this day, questions around the best type and dose of antenatal steroids require further study.

Only 2·5% of trials included in the Cochrane Central Register involve neonates,[10] the number of registered trials involving neonates is diminishing,[11] and about half of studies in neonatology did not adequately test their primary endpoint or did not complete patient enrolment.[12] This gap in research is also apparent in funding databases. A search of the European Commission database of research funding (CORDIS) in the Horizon programme on July 18, 2023, retrieved 44 funded projects in adult intensive care and six funded projects in neonatal intensive care. Most neonatal trials on assisted ventilation—arguably the most pivotal life-saving therapeutic intervention in neonatal intensive care—are unfunded and performed during regular working hours without any additional support.[13]

Neonatology has an immediate impact on short-term and long-term health yet industry support for research and development in neonatology pales in comparison to the support seen in adult critical care, oncology, and infectious disease. Regrettably, we have no formal comparative data to prove this claim; it is our shared opinion that neonatology has not benefitted from extensive investments and commitments to preclinical and clinical research because it treats a relatively small patient population and has unique difficulties related to patient size, feto–neonatal physiology and disease pathobiology, and patient recruitment for studies. The mother–baby dyad demands special consideration, and research in the perinatal space is challenging. Ultimately, the value of newborn life is not universally recognised or considered in the same way. Some cultures value newborn and older children differently, and families respond to newborn deaths in many ways. Across various areas and contexts, cultural and social values have shaped how societies perceive the importance of innovating neonatal medicine to reduce newborn mortality.

Neonatology sees patients in emergency situations and in need of critical care, and many current treatments of acute neonatal disorders (such as acute respiratory distress syndrome [ARDS], septic shock, and multisystem organ dysfunction and failure) were informed by adult critical care research (panel 1). Although neonatology benefits from adult medical research, neonatal and adult medicine can learn from each other. For example, inhaled nitric oxide was originally developed for newborn patients but now has an established role in the perioperative intensive care of children and adults undergoing cardiothoracic surgery and for patients with severe respiratory failure.[14,15] Pronation, originally introduced in adults with severe ARDS, also improves gas exchange in infants requiring respiratory support for evolving bronchopulmonary dysplasia.[16] The similarities in lung physiology and related mechanics between bronchopulmonary dysplasia in neonates and chronic obstructive pulmonary disease in adults suggest that pronation might benefit adults with acute chronic obstructive pulmonary disease exacerbations.[16]

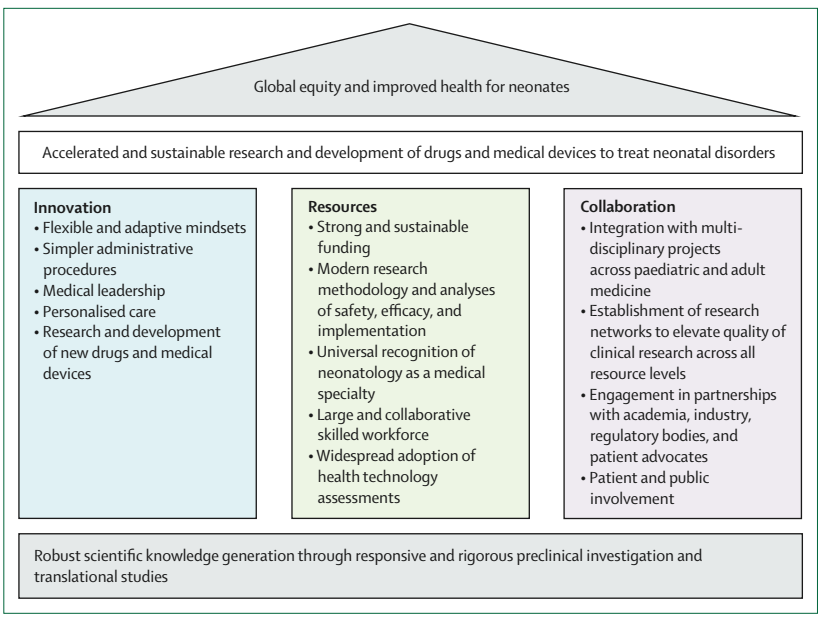

Figure 1: **Advancing neonatal medicine as an innovative medical specialty**

Preclinical and translational research for neonatal disorders[17] is insufficient because funding and public attention are inadequate. Although treatment of neonatal disorders would have a high intrinsic value, newborn health is not perceived as a major public health issue, and public attention is usually directed to more prevalent disorders (eg, metabolic syndrome, cancer, and hypertension) and communicable diseases. Yet improving newborn health care has great public health value because newborn health affects the whole lifespan. Last, but not least, excessively stringent regulations and procedures from regulatory agencies, institutional review boards, and governments inhibit efforts to improve the understanding of basic disease mechanisms: regulations are designed to protect the patient during the process of innovation, but they do not protect patients from the absence of innovation. It is clear that insufficient knowledge coupled with an inadequate toolbox of efficacious drugs and medical devices is causing harm to neonates.

Rates of preterm birth, birth complications, severe malformations, and neonatal infection have remained unchanged in every region of the world for the past decade.[18] About one in ten newborn infants requires expert medical care, and most childhood deaths occur in

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***Panel 2:* Methods applied by the *Lancet Child & Adolescent Health* Commission on the future of neonatology**

Five neonatologists and one public health physician from Africa, Asia, the Americas, Europe, and Oceania formed the Steering Committee. In line with the Lancet Group policy on competing interests, the Steering Group invited Commission members to contribute to prespecified working groups with dedicated aims. The final Commission had 29 members from various professional backgrounds who brought a balanced representation of sex and diverse representation of geographical region, professional background, age, and academic seniority. In addition, about 100 individuals from key stakeholder groups (neonatologists, paediatricians, paediatric surgeons, maternal and fetal medical specialists, nurses and other allied health professionals, regulators, policy makers, basic scientists, former patients, and family representatives) were invited to contribute as advisers; they are listed in the appendix (pp 2–3).

The Commissioners worked across five working groups to reflect on and report recommendations for specific questions:

1 How can neonatology achieve an efficient research and development pipeline for neonatal medicines?
2 How can neonatology achieve an efficient research and development pipeline for neonatal medical devices?
3 Why is neonatal research and development important for population health and wellbeing?
4 How can neonatology promote collaboration in neonatal research and development?
5 How can neonatology strengthen and enhance the recognition of neonatal research and development as a global necessity?

Each working group met virtually and worked independently. Their reports informed the Commission's draft recommendations for institutional review boards, ethics committees, and regulatory agencies; industry; physicians and other health-care professionals; governments, universities, and academic medical centres; and former patients' and family representatives. The final recommendations were derived through the Quaker-based consensus technique,[8] which included open discussions with active listening and sharing of information and questions, with results eventually attributed to all participants.
The Commissioners and editorial team held two plenary meetings, the costs of which were shared between Commissioners and *The Lancet Child & Adolescent Health*.

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the first month of life at least in part because of lingering uncertainty across many fundamental aspects of newborn health care, such as optimal nutrition or ventilatory and haemodynamic support.[3] Most of the 2·3 million children who die in their first month of life every year are born in low-income and middle-income countries (LMICs)—it is here that the starkest consequences of continued inaction will be seen.

Although survival has improved for many neonatal disorders, long-term adverse neonatal outcomes remain prevalent, and long-term sequelae of neonatal disorders, including non-communicable diseases in adulthood, are increasingly recognised. Neonatal disorders, some of which start before birth and continue to evolve well after the neonatal period, are insults that can affect health for many years to come (figure 2). Failure to innovate in the diagnosis and management of neonatal disorders therefore has long-term consequences. In terms of disability-adjusted life-years (DALYs)—ie, the sum of the years of life lost due to neonatal mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population[19]—neonatal interventions have a striking impact because management in the neonatal period determines health and economic outcomes across the lifespan and affects quality of life for many decades.[20]

With little improvement in preventing long-term adverse outcomes, insufficient research and development also creates ethical dilemmas. For example, saving the life of a child who will live with a disability might have relevant consequences for the individual, the family, and society as a whole. However, it is disability-free survival that generates quality-of-life, resource, and productivity benefits through adulthood. Neonatal intensive care and surgery can save lives but cannot yet prevent long-term adverse effects, and adequate research and development that draws on state-of-the-art biotechnology is urgently needed to close this gap.

Value-based neonatology for health and wellbeing across the lifespan

For many families, a healthy newborn child brings happiness, whereas the death of a newborn is devastation. There is growing recognition of the trans-generational benefits of newborn health.[21] On a societal level, newborn health drives national productivity, resilience, and prosperity.

Striving to understand the mechanisms of newborn diseases is necessary to design medicines and devices that improve survival, reduce comorbidities that affect quality of life, identify modifiable early-life factors to improve personal and population health, and develop effective preventive policies and interventions. The cost of this research is minimal compared with the costs of deteriorating population health across the lifespan. Yet an objective appreciation of the value of improved neonatal medicine—improving quality of life, productivity, and prosperity over the entire lifespan—is not apparent with a traditional measure of success. By contrast, a values-based approach to neonatology provides a framework for cost-effective, evidence-based neonatal care grounded in patient values and ensures that health-care success mirrors the societal benefit of that success.[22] The advantages of adopting a values-based approach to neonatology are clear when considering the neonatal disorders with lifelong impact (panel 3).

Around the world, approaches to newborn health are fragmented, services are siloed, and treatments are not based on high-quality basic and translational science. Yet a child's health status during the neonatal period influences health throughout that child's life course; for example, respiratory and cardiovascular disorders are prevalent among people who were born preterm or were critically ill during the perinatal and neonatal periods.[32,34–36] By failing to improve newborn health services and treatments, these risk factors will continue to go undetected and untreated, and we will squander the opportunity to enhance human capital through early-life interventions.[37,38] Value-based neonatology would foster a

culture of improving diagnosis and treatment of neonatal disorders—not only for the health and wellbeing of the child but also to mitigate morbidity in adulthood and premature mortality. To seize this opportunity to improve population health with global and trans-generational benefits requires the establishment of sustainable research and development pipelines that are linked to reliable public health policies rooted in galvanised public support for neonatal medicine.

Development of new neonatal drugs and medical devices

Neonatal drugs

Surfactant[39] and inhaled nitric oxide[40,41] are the only neonatal therapies that have been specifically developed for neonates. Many neonatal diseases are managed without effective and targeted neonatal therapies.[42] Moreover, more than 95% of medicines used in neonates are prescribed off-label or off-licence, which increases the risk of adverse effects.[4,43]

The most common causes of neonatal death and adverse outcomes, accounting for about 76% of neonatal deaths, are acute respiratory failure, bronchopulmonary dysplasia, hypoxic-ischaemic encephalopathy, malformations, necrotising enterocolitis, and severe infections.[44] However, our poor understanding of the pathophysiology underlying these conditions hampers the development of appropriate treatments. For example, current preventive and therapeutic interventions for bronchopulmonary dysplasia and necrotising enterocolitis lack sufficient evidence of efficacy, safety, and disease specificity. None of the promising molecules designed to protect the brain from hypoxic-ischaemic encephalopathy has reached clinical practice.[45] Medications for septic shock and severe infections rely on experience accumulated in adult critical care, with no high-quality data specifically obtained in newborn populations.

The development of new medicines for neonates remains limited despite incentives to the pharmaceutical industries, such as the US Food and Drug Administration's Best Pharmaceuticals for Children Act and the Safety and Innovation Act.[43] Only three of the 175 paediatric medicines granted a new paediatric indication, dosage, or age group by the European Medicines Agency in the period from January, 2007, to December, 2019, were specifically for neonatal disorders.[46] The research and development of several drugs for neonates was stopped despite encouraging preclinical or clinical studies.[7,47–60] Figure 3 highlights a few examples of neonatal drugs with delays due to regulatory, commercial, or industrial (ie, manufacturing) issues rather than purely scientific issues.[61,62]

Delays and difficulties in the development and implementation of surfactant therapy for preterm neonates capture the broader challenges in innovation for neonatology. Arguably the most impactful neonatal medication, surfactant was initially evaluated in basic science, animal, and human translational studies that culminated in comprehensive clinical trials in the 1980s (panel 4).[39,69,74,75] Surfactant's research and development journey would have been very different in the current regulatory environment.[76]

Surfactant has only recently undergone the necessary dose-finding studies, and the optimal dose was determined to be 200 mg/kg in preterm babies with respiratory distress syndrome due to surfactant insufficiency (the optimal dose is still unknown where there is relevant lung inflammation consuming surfactant).[77,78] Nevertheless, the optimal dose remains uncertain for some patient subgroups,[77,78] and challenges with disseminating these new findings risks incorrect dosing in clinical practice.[79,80] Indeed, about 42% of

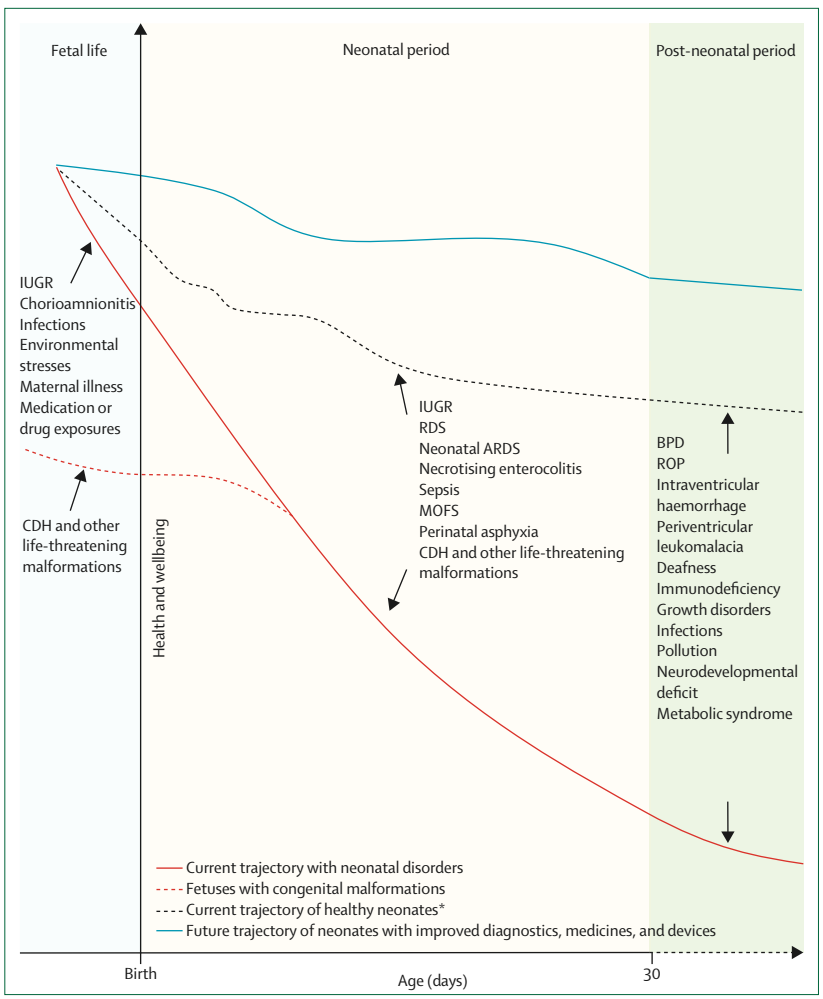

Figure 2: **Schematic representation of the lifetime trajectory of health and wellbeing of neonates with available neonatal medicine and the potential impact of future improved neonatal medicine**
Neonatal disorders often have long-term sequelae that can affect health and wellbeing along a continuum. Shown are disorders that can occur prenatally or postnatally and the long-term chronic consequences occurring after the first month of life and beyond. ARDS=acute respiratory distress syndrome. BPD=bronchopulmonary dysplasia. CDH=congenital diaphragmatic hernia. IUGR=intrauterine growth restriction. MOFS=multiple organ failure syndrome. RDS=respiratory distress syndrome. ROP=retinopathy of prematurity. *Healthy neonates include some sick neonates who are efficaciously treated with available neonatal medicine.

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See **Online** for appendix

Panel 3: Examples of neonatal disorders with lifelong impact

- Gestational diabetes increases the risks of congenital anomalies, stillbirth, neonatal respiratory failure, and prematurity; the incidence of gestational diabetes is highest in populations with high obesity prevalence.[23,24]
- In comparison to people born at full-term, those born preterm are at high risk of early death and morbidities in adulthood, such as cardiovascular, respiratory, metabolic, renal, neurological, and psychiatric disorders.[25]
- Adverse experiences in infancy disrupt normal developmental trajectories and further increase the adverse effects and risks of health-harming behaviours, environmental exposures, and non-communicable diseases in later life.[25]
- Perinatal changes in the microbiome can alter neonatal physiology, influence the need for neonatal intensive care, and even affect health later in life.[26,27]
- Transient tachypnoea of the neonate—the mildest of neonatal respiratory disorders—has a relevant burden of care and is associated with recurrent wheezing, asthma, exercise intolerance, and the early development of chronic obstructive pulmonary disease later in life.[28–31]
- Bronchopulmonary dysplasia can affect growth, respiratory, and general health across the whole lifespan.[32]
- Newborn infants affected by congenital disorders, such as congenital diaphragmatic hernia, often have relevant mortality and, if they survive, major long-term neurological, gastrointestinal, and respiratory problems.[33]

For some of these examples, a prenatal preventive or therapeutic strategy could theoretically be more advisable than an early neonatal intervention.

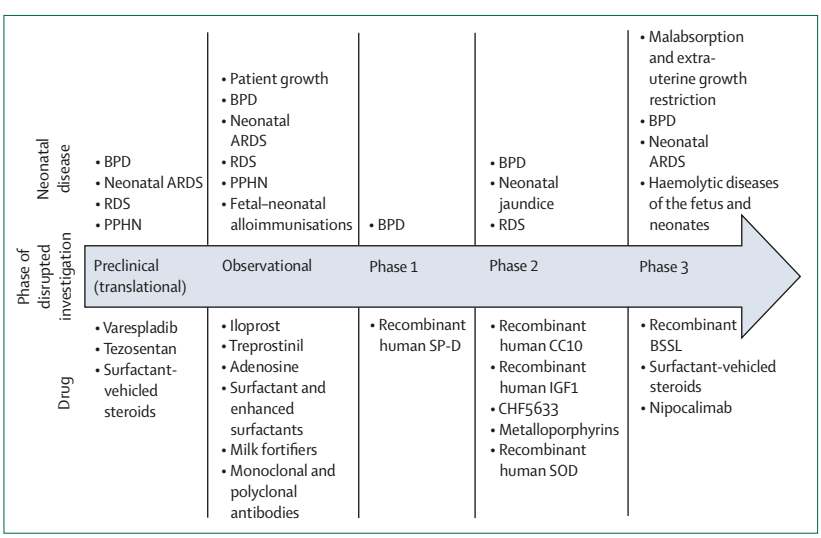

***Figure 3*: Examples of drug development for neonatal diseases that was stopped or excessively slow, despite promising results**

Drugs are listed with potential indications in parentheses: varespladib (BPD, neonatal ARDS, and RDS [primary surfactant deficiency]); tezosentan (PPHN, particularly due to meconium aspiration); surfactant-vehicled steroids (BPD and neonatal ARDS); iloprost, treprostinil, and adenosine (PPHN); surfactant and enhanced surfactants (neonatal ARDS and RDS); milk fortifiers (patient growth); monoclonal and polyclonal antibodies (fetal–neonatal alloimmunisations); recombinant human SP-D, recombinant human CC10, recombinant human IGF1, and recombinant human SOD (BPD); CHF5633 (RDS); metalloporphyrins (neonatal jaundice); recombinant BSSL (malabsorption and extra-uterine growth restriction); and nipocalimab (haemolytic diseases of the fetus and neonates).[7,47–60] Surfactant-vehicled steroids, such as budesonide, have been tested in several high-quality, investigator-initiated, clinical trials without reaching industrial (ie, manufacture and distribution) development. Conversely, steroids other than budesonide have only been investigated in animals. Many other drugs are not included because they have been studied without industry contribution (ie, investigator-initiated clinical trials). ARDS=acute respiratory distress syndrome. BPD=bronchopulmonary dysplasia. BSSL=bile salt-stimulated lipase. CC10=club cell secretory protein 10. IGF1=insulin-like growth factor 1. PPHN=persistent pulmonary hypertension of the neonate. RDS=respiratory distress syndrome. SOD=superoxide dismutase. SP-D=surfactant protein-D.

For the list of **essential medicines** see https://list.essentialmeds.org

clinical trials of surfactant in the past decade have used the wrong dose or reported it inaccurately.[81]

A European consensus in 2021 highlighted the need for further research to optimise replacement surfactant treatment for term and preterm neonates[56] and to explore new indications, including neonatal ARDS.[56] Importantly, however, this further research must extend to LMICS, where most of the world's children are born.[82] WHO has designated surfactant an essential medicine, but access to surfactant in LMICs is restricted due to the high cost and insufficient medical training required for its administration.[83] Surfactant research in LMICs, and engagement of LMICs with neonatal research and development more broadly, is important and necessary but will require overcoming socio-cultural and economic issues.

Another reason promising neonatal drugs do not complete the research and development pathway and enter clinical practice is that preclinical data underpinning safety and efficacy studies have sometimes been overlooked, increasing the risk of high costs, safety concerns, and ultimately failure at efficacy evaluation.[45,56] Medicines should not reach the clinical trial stage of development without rigorous clinical pharmacology or pharmacokinetic, pharmacodynamic, and dose-finding studies. Anaesthesia, analgesia, and sedation are widely provided to critically ill neonates even though safety and efficacy data have not been systematically collected and examined. Results of animal studies raise the concern for potential long-term consequences of some of the most common analgesic and sedative medicines for neonates.[84–87] Clinical studies have confirmed the safety concerns with prolonged use of these medicines, particularly in preterm neonates,[88,89] which has led to an FDA warning about use of anaesthesia or sedation in neonates and infants.[90] This creates a dilemma: pain is harmful for neurodevelopment,[91] but the clinical evidence base to support our only pharmacological options to reduce that pain is inadequate. Therefore, do the potential risks of an intervention outweigh the adverse developmental effects of the problem?

Currently, EU and US regulations require trial sponsors to specify paediatric investigation plans (PIPs) or paediatric study plans. However, very few of these plans relate specifically to neonates.[46] Medicinal products studied by

academic researchers without industry involvement have rarely reached licensed status, partly because of disinterest by pharmaceutical companies, but also because these studies have not met the quality standards required for regulatory approval. Effective research and development for neonatal medicines requires integrated contributions from several players, including industry, academic medical centres and universities, clinicians, basic scientists, methodologists, ethicists, public health specialists, and others.

Neonatal medical devices

Medical devices are required for the increasing sophistication of intensive care. Electrocardiogram, oxygen saturation, respiratory rate, and perfusion index are examples of continuous monitoring devices that are integral to routine critical care. Amplitude-integrated electroencephalogram, multisite near-infrared spectroscopy, invasive blood pressure measurements, and end-tidal carbon dioxide sensors are equally essential in the management of severely ill patients.[92]

A small number of medical devices have been remarkably successful in serving the health-care needs of the neonatal population. Phototherapy and incubators are rare examples of medical devices that were specifically developed for neonates. Transcutaneous bilirubinometry was developed for infants and is sufficiently accurate to screen or monitor serum bilirubin in a newborn population of any ethnicity, including neonates undergoing phototherapy.[93–96] Transcutaneous blood gas monitoring has been successfully developed for critically ill neonates and avoids invasive blood sampling.[97]

In general, however, medical devices and drugs for neonatal care share many of the same research and development obstacles that hinder innovation. Sleep–wake cycle characteristics, heart rate variability, volumetric capnography, and behavioural signs of stress or pain are just some of the physiological parameters that are monitored as part of neonatal intensive care, yet they all await technological innovation to move intensive care practice from one-size-fits-all protocols to personalised neonatal critical care. Medical devices that are used in neonatology but await further technological innovation and more widespread availability are listed in table 1.

Advances in medical device technology tend to be driven by unmet needs in adult critical care. Some of the technologies developed for adult critical care have been adapted for neonatal critical care. Recent examples include point-of-care ultrasound, whole-body hypothermia, and renal replacement therapy technologies.[98–100] However, not all technological advances in the adult critical care space transfer into the neonatal critical care space. For example, continuous glucose monitoring is available in adult critical care and would benefit critically ill neonates, but we suspect that its adoption in neonatal critical care is hampered by marketing decisions and regulatory requirements.[101] Other useful medical technologies cannot be widely implemented in the clinic without interest and support from industry—lung ultrasound to guide surfactant replacement is one example.[98]

Despite the shared features of neonatal and adult critical care (eg, organ failure and perioperative support), high-end technologies that are taken for granted in adult critical care are either not available (eg, advanced haemodynamic monitoring) or unsuitable (eg, CT scans) for neonates. Volumetric capnography, laryngeal masks, and other

Panel 4: The history of surfactant

Surfactant is arguably the most impactful neonatal drug and one of the few that was specifically developed for neonates. Surfactant replacement obtained striking results in terms of improved major outcomes, but has a history that seems to be unrepeatable. In fact, its development was based on preclinical and translational data that would be very difficult to produce now. Furthermore, the clinical studies were much simpler and quicker than what it is currently possible due to regulatory and other requirements.

The first step was the comprehensive description of hyaline membranes observed in deceased infants, which was originally reviewed by Tran-Dinh-De and Anderson[63] and then built on by Claireaux[64] in 1953 using numerous neonatal autopsies. This led to the designation of "hyaline membrane disease" as cause of death. Yet this first step would be impractical now, given the decreasing number of neonatal autopsies.[65] The reduction in the number of autopsies might be due to undervaluing of the process by clinicians and consequent failure to adequately explain to families the value of such a procedure; yet parents still prefer to get an autopsy to understand cause of death of the infant and to help prevent further deaths.[66]

At the same time, a consensus meeting of key opinion leaders, including Virginia Apgar and Mary Ellen Avery, named the disease "idiopathic respiratory distress syndrome", underlining the difficulty and the imprecision of its diagnosis and imaging.[67] Of note, much of this imprecision reported in 1960 remained until the advent, in 2020, of point-of-care lung ultrasound with much improved accuracy.[68] By the early 1960s, Avery and Mead in the USA and Robertson in Sweden discovered the association between reduced surfactant and respiratory distress syndrome.[69,70] This discovery was followed by crucial preclinical studies in which surfactant was extracted from adult animals and injected into preterm ones, showing its effect in terms of lung mechanics and gas exchange and so eliminating the last doubts about the causal link between surfactant deficiency and respiratory failure.[71,72] Current regulations considerably restrict the use of animal models and would make these studies extremely challenging, preventing the full understanding of pathobiology of respiratory distress syndrome.

Finally, Fujiwara and colleagues[39] in 1980 and Berggren and Curstedt[73] in 1984, described the first clinical cases of neonatal respiratory distress syndrome treated with artificial[39] or animal[73] surfactant. These were simple, uncontrolled case series in which experimental drugs were administered and can be approximated to first-in-human trials; this type of study would currently require substantial funding to cover insurance and administrative costs, which is rarely provided for rare disorders such as neonatal diseases. Additionally, the present regulatory framework would require much more preclinical data than those produced by Fujiwara and colleagues and Berggren and Curstedt in the 1980s,[39,73] or even for inhaled nitric oxide in the 1990s.[40,41] Regulatory agencies are currently more focused on the risks of research than on the risks of not doing research, which, when combined with increasing barriers for preclinical animal studies, would have created a much more challenging research environment and surfactant development probably would not have been realised. As a consequence, thousands of deaths from respiratory distress syndrome would not have been averted.

	Non-invasive	Minimally invasive	Invasive
Biochemical monitoring	..	Point-of-care micro-volume blood cell count and biochemical assays	Technologies for continuous blood gas monitoring on arterial lines
Airways and respiratory management	Volume-controlled resuscitation device; anatomically accurate 3D face masks; bedside neonatal imaging devices (eg, electrical impedance tomography and derived tools); practical device to measure lung mechanics and airway resistance in non-intubated infants; software and tools for calculation of mechanical power	Smaller laryngeal mask; smaller videolaryngoscope; tools for measuring oesophageal and transpulmonary pressure; volumetric capnography adapted to smaller patients; capnography adapted to non-conventional ventilation modes	More practical tools for fetal tracheal occlusion therapy; smaller bronchoscopes
Haemodynamic monitoring	Electrical cardiometry; heart rate variability analysis	Trans-oesophageal doppler	Pulse pressure analysis; thermodilution techniques
Neurological monitoring	..	Sleep cycle monitoring; amplitude-integrated electroencephalography	..
Diagnostics	Ultraportable ultrasound devices; ultra-high frequency probes	Miniaturised CT scan and MRI tools	..
Nutrition	Low-volume milk composition analysis for personalised nutrition; storage or delivery solutions to ensure safety of milk while preserving nutrients	Better milk pump technologies	..
Biomaterials	..	..	Diaphragm patch that grows with the patient; 3D bioprinting of trachea or oesophagus; better centrally inserted venous catheters, specifically dedicated to neonates and tools for their fixation and care; better (heparin-coated or citrate-coated) circuits or devices for extra-corporeal membrane oxygenation, continuous renal replacement therapy, and other extracorporeal therapies (eg, cytokine removal and blood purification)
Data surveillance	Telemedicine tools for diagnostics in remote areas	..	..
Intervention-guiding devices	High-fidelity simulation tools; eye-tracking tools	..	..

Table 1: **Medical devices in neonatology that need further technological innovation or more widespread clinical availability**

supraglottic devices need to be adapted on a case-by-case basis to fit the smallest patients. Indeed, medical devices for neonatal critical care must be designed with specific considerations of physiology—not only size, but the immature and rapidly developing organ systems, such as neonatal skin and transitional circulation through the patent ductus arteriosus, require careful consideration. Miniaturisation is a major barrier in medical device development, especially in relation to advanced wearable and wireless technologies, but it can be overcome with adequate investments. The recent development of dedicated neonatal electrical impedance tomography systems that use wearable technology shows the potential and challenges.[102]

Further challenges of clinical trials for medical devices relate to the intervention's technical complexity, duration, and staff training requirements to ensure clinicians understand not just how to deliver the intervention but also how to manage and maintain the device. This is the main difference compared with pharmacological trials in which the intervention (ie, a drug) must only be administered, usually without the need for training, management, or titration, which medical devices need. From monitoring to ventilation, renal replacement therapy, and extracorporeal membrane oxygenation, medical devices operate across multiple modalities and parameters that affect the efficacy and safety of the intervention. In this context, it is perhaps not surprising that none of the health-related projects funded by the European Institute of Technology is dedicated to neonatal medicine.

For more on the **health-related projects of the European Institute of Technology** see https://eithealth.eu/our-impact/spotlight

The overwhelming extent of unmet needs in neonatal critical care ought to drive technological innovation. For example, the technology behind transcutaneous bilirubinometry has the potential to be further developed to measure blood glucose non-invasively, thereby avoiding the need for painful heel prick.[103] Since bilirubin and glucose assays are most common clinical biochemistry tests for neonates, development of this technology would avoid one of the most common painful invasive procedures in nurseries worldwide. Examples of existing technology that could address unmet needs in neonatology if resources were committed to dedicated research and development are listed in table 2.

Barriers in medical device development can be overcome. The device for neonatal extracorporeal renal replacement was approved by the FDA without randomised trial data. Approval was based purely on observational data in Italian and US registries[104] that have since been replicated in

France.[105] Although the approval addresses an unmet clinical need for critically ill neonates, it also highlights striking differences with other technologies (some already in widespread use) that have not been approved by the FDA because randomised trials had not been done. For example, high-frequency oscillatory ventilation (HFOV), delivered either invasively or non-invasively,[106,107] is an accepted mode of respiratory support for neonates, particularly those with severe respiratory failure not responding to conventional approaches. Several HFOV devices are marketed in the global market,[108] but only two devices are available in the USA, both of which were developed more than three decades ago. The failure to approve modern HFOV devices relates to FDA requirements for prohibitively expensive documentation of safety and efficacy in clinical trials. This high barrier to entry into the US market is an impediment to state-of-the art newborn care and is ethically unacceptable. Similarly, a panoply of non-invasive ventilation interfaces exists for neonates, each with their mechanical and physiological peculiarities,[109–113] and they are absolutely needed to increase the effectiveness of non-invasive respiratory support. However, the importance of interfaces is under-recognised, and their availability is uneven worldwide.

These disparities need attention to ensure that all neonates benefit from innovative medical devices, irrespective of local marketing conditions and manufacturing facilities. Financial issues related to the initial purchase and ongoing cost of disposables and to staff training on device use and maintenance are particularly challenging in LMICs and has already culminated in inequitable access to useful medical devices and inequitable opportunities for staff to acquire the skills to use the devices.

Countries in the EU are already experiencing similar difficulties in medical device availability. A 2017 EU Medical Devices Regulation (2017/745) replaced three previous directives[114] to ensure high safety and quality standards for medical devices and to harmonise data across EU member states. Although the intention is laudable, the associated administrative and bureaucratic burden has adversely affected small and medium enterprises that develop products for use in neonatal clinical care. All European paediatric and perinatal scientific societies, as well as parent representatives' associations, have signed an open letter to the EU Commission raising the concern that, because of this new directive, several essential neonatal medical devices have become or will become unavailable.[115] Examples of essential medical devices at risk are the tracheal occlusion balloons for fetuses with congenital diaphragmatic hernia, atrial septostomy catheters for neonates with congenital heart defects, fluid bags for neonatal renal replacement therapy, and extracorporeal membrane oxygenation pumps for neonatal ARDS, acute kidney or heart failure, septic shock, and acute metabolic diseases. In response to this letter, the EU Commission extended the time allowed to comply with the new directive. Nonetheless, this extension is not a permanent solution, and the medical community and industry are worried about not being heard enough by governments and regulatory agencies, with a consequent risk of a shortage of essential neonatal medical devices.

Notably, regulatory agencies have shown willingness to compromise by permitting emergency use of much-needed tools. For example, the new directive forced an end to the manufacture of balloons used for fetal tracheal occlusion to treat congenital diaphragmatic hernia in utero. The French regulatory agency then authorised the compassionate use of a new balloon pending the attribution of the industrial CE mark. This device is better than the previous balloon in terms of safety and logistics because it can be deflated when the patient is close to a strong magnetic field, such as that of MRI devices.[116] This technical feature facilitates the therapeutic intervention (ie, the fetal tracheal occlusion) because in the case of an emergency delivery, the tracheal balloon can easily be removed with MRI and the neonate can be intubated and ventilated. Without this feature, the emergency delivery of these babies would require much more complex and invasive resuscitative procedures (eg, ex utero intrapartum treatment or emergency vessel cannulation for extracorporeal membrane oxygenation). The decision to allow the use of this tracheal balloon exemplifies the ability of regulatory agencies to provide sufficient and rapid review and support for neonatal interventions to treat specific diseases, such as severe congenital

	Non-invasive	Minimally invasive	Invasive
Biochemical monitoring	Transcutaneous glucose, pH, and lactate monitoring; salivary biochemical assays	..	..
Airways and respiratory management	Thin-walled endotracheal tube; neonatal endotracheal tube for independent lung ventilation; wireless or contactless lung mechanics assessment device	Ventilation or perfusion assessment tools; point-of-care inflammatory biomarkers assays	Repeatable and non-invasive methods to assess lung function in ambulatory care settings (follow-up)
Haemodynamic monitoring	Wireless, contactless, or wearable sensors; microcirculation visualisation tools; smart trending monitoring and predictive software for neonates	..	..
Neurological monitoring	Bedside MRI and CT scan; non-invasive stress and pain monitoring	..	..
Diagnostics	AI-driven cry analysis	..	..
Nutrition	Personalised fortification based on milk analysis and infant growth; AI-driven nutrition protocols	..	..
Data surveillance	Big data analysis in the NICU; AI-driven data collection and analysis	..	..
Intervention-guiding devices	Augmented reality to guide and train procedures; robotised procedures	..	..

NICU=neonatal intensive care unit.

Table 2: **Medical technologies that could address unmet needs in neonatology but require medical device research and development**

	Indonesia	Mexico	South Africa
Population, million	284	134	65
Total NICU beds in the country	514	5660	500
NICU beds per million inhabitants	1·8	42·2	7·7
Patient-to-nurse ratio in NICU	2 to 1	5 to 1	4 to 1
Oxygen availability	100%	66%	95%
Oxygen blender availability	30%	36%	70%
SpO_2 monitor availability	65%	64%	70%*
Caffeine and surfactant availability	≤5% to 85%	71%	0·7%
Participation in neonatal registry	No	No	Some†
Neonatal health-care system	95% public	80% public, 20% private	70% public, 30% private
Public support for neonatal research and development (public research grant availability)	<5%	No	Very little
Academic support for neonatal research and development	Some	Some	Some
Industrial support for neonatal research and development	Limited	No	No
GDP per capita, ×US$1000	4·8	17·4	6·0

These data were generated by the Commission working groups. GDP=gross domestic product. NICU=neonatal intensive care unit. SpO_2=peripheral oxygen saturation. *SpO_2 monitors are often shared between neonates so continuous monitoring is not always provided. †Some units contribute to the Vermont Oxford Network.

***Table 3*: Neonatal research, care, and basic infrastructure in Indonesia, Mexico, and South Africa**

diaphragmatic hernia. This mindset is independent of resources currently available to the regulatory bodies and shows how opportunities can arise from adversities.

Global equity for neonates

Most neonatal deaths occur in LMICs[117,118] and in babies born at term.[119] Half of the infants who die in LMICs do so within 24 h of birth.[117,118] Estimates suggest that at least 267 208 (95% CI 112 000–422 415) babies from 128 LMICs died from preventable causes in 2020, equivalent to a 6·8% (95% CI 2·8–10·7) increase in the total number of expected infant deaths,[120] exemplifying how many newborn lives were lost even in respect to the losses occurring because of the pandemic. For example, the vast majority of neonatal units in sub-Saharan Africa cannot provide blended oxygen therapy, which worsens such vital outcomes as severe retinopathy of prematurity and perhaps survival.[121]

The burden of child deaths is inversely proportional to the resources of the country in which they occur: the average gross domestic product (GDP) lost per child death in the first 5 years of age is equivalent to 3·7% of the GDP for high-income countries (HICs) and 7·1–8·4% for LMICs.[122] Some of these negative outcomes would be preventable with adequate pregnancy care and perinatal follow-up, although we need to acknowledge the variability among LMICs because of economic, socio-cultural, and political contexts. Examples of how neonatal research, care, and basic infrastructure differ between LMICs are listed in table 3.

Research and development projects in LMICs are not usually considered profitable for industry. Most neonatal medicines and devices used in LMICs were originally developed and evaluated in research projects in HICs. The results of these trials were later disseminated to LMICs, which have vastly different practices, resources, and patient characteristics. Safety and efficacy data from clinical trials in HICs are not always directly generalisable to LMICs. In some cases, interventions are only life saving in settings with trained staff and support services. Antenatal steroid prophylaxis is an example of how research has exclusively benefited clinical practice in high-resource settings.[123,124] Antenatal steroids are a ubiquitous and efficacious treatment in high-resource settings, but they could be harmful in LMICs, possibly because of increased rates of maternal infection.[125] Intraocular anti-VEGF therapies delay progression of retinopathy of prematurity in high-resource settings, but might not be effective in settings without robust screening for retinopathy of prematurity and provision of supplemental oxygen.[126] The HELIX study[127] found increased mortality in babies with hypoxic-ischaemic encephalopathy who received therapeutic hypothermia in Bangladesh, India, and Sri Lanka. However, therapeutic hypothermia has been successfully and safely applied, even using low-technological devices, in some resource-constrained settings in Africa.[128] These observations highlight the importance of generalisability in clinical studies, which is achieved when considering individual host responses to critical illnesses,[129,130] resources, and cultural and social aspects of holistic, family-centred care.

Many socioeconomic, cultural, financial, and political challenges differ between LMICs and HICs. These challenges also include regulatory barriers, advocacy issues, resistance from stakeholders, and bureaucratic complexities that influence research, as well as health-care problems affecting LMICs. To better understand the barriers and obstacles to neonatal research and development in LMICs and the challenges in adopting and implementing innovation that has been developed in HICs, we conducted focused interviews with five commissioners and 28 advisers, representing 30 countries (15 advisers represented LMICs). We also enquired whether innovation in LMICs could benefit the global neonatal community and how colleagues in LMICs can be supported in completing high-quality research. Details of the survey methodology are presented in the appendix (pp 5–9). Our findings are presented in figure 4.

Provision of adequate supplies of neonatal medicines and devices and sustainable investment in equipment purchase, maintenance, and training are considerable challenges in LMICs, not just in neonatology but for all of health care (eg, anti-HIV medicines). Organisational and financial difficulties also restrict access to scientific resources and training, which is necessary for collaborations between HICs and LMICs.[131] LMICs have the greatest burden of skills shortage. 29 African countries have fewer than five neonatologists, and more than half of neonatal intensive care units (NICUs) in Latin America are staffed by paediatricians without adequate neonatal

critical care training. By comparison, according to the French Society of Neonatology and the French Society of Perinatal Medicine, France has 67 tertiary referral NICUs that are fully staffed by clinicians with at least 1·5 years of neonatal critical care-specific experience coupled with further training in related domains such as paediatric critical care and paediatric cardiology. LMICs have few units that can provide care for critically ill infants, a situation that mirrors some HICs before the importance of neonatal medicine was recognised. Another difficulty in LMICs is the basic infrastructure that prevents the provision of certain therapies. For example, electricity, oxygen, and other gas supplies might be unstable.

Inequitable access to life-saving care and basic necessities such as oxygen and water was glaringly brought to light during the COVID-19 pandemic, when only 67% of African countries had access to any form of continuous positive airway pressure.[132] Furthermore, when conflicts or natural disasters occur, the immediate priority is the delivery of essential neonatal care (eg, hand hygiene, temperature maintenance, umbilical cord and skin care, basic resuscitation, and breastfeeding), whereas training, education, and research assume less importance. Funding for research in LMICs is frequently directed towards HIC-based researchers. In the absence of clear strategies for knowledge and technology transfer, global inequities will persist and the opportunities to build on local expertise will continue to be wasted.

These difficulties notwithstanding, neonatal medicines and devices that are developed for or in LMICs stand to benefit the global neonatal community. Innovative thinking to overcome adversity could result in novel approaches that would never have been considered in resource-rich regions. The volume of neonatal patients in many LMICs is an enabling factor for neonatal clinical research as it can provide much higher sample sizes. For example, in South Africa, the incidence of hypoxic-ischaemic encephalopathy is estimated to be 8·7–15·2 per 1000 livebirths at term, compared with 1–8 per 1000 in HICs.[133] Similarly, in one Nigerian tertiary hospital, the fatality rate among babies with hypoxic-ischaemic encephalopathy was up to 25%.[134] These examples showcase an opportunity for both large-scale research and the discovery of new treatments. It is crucial for research to be done in both HICs and LMICs to ensure relevance to different populations and resource levels, and based on local priorities. Meaningful collaboration between researchers in high-resource and low-resource settings can ensure that knowledge, resources, skills, and findings are shared and implemented equitably.

Strengthening cross-disciplinary collaboration, preclinical research, and personalised neonatology

Neonatal care benefits from cross-disciplinary awareness, especially from adult intensive care medicine,

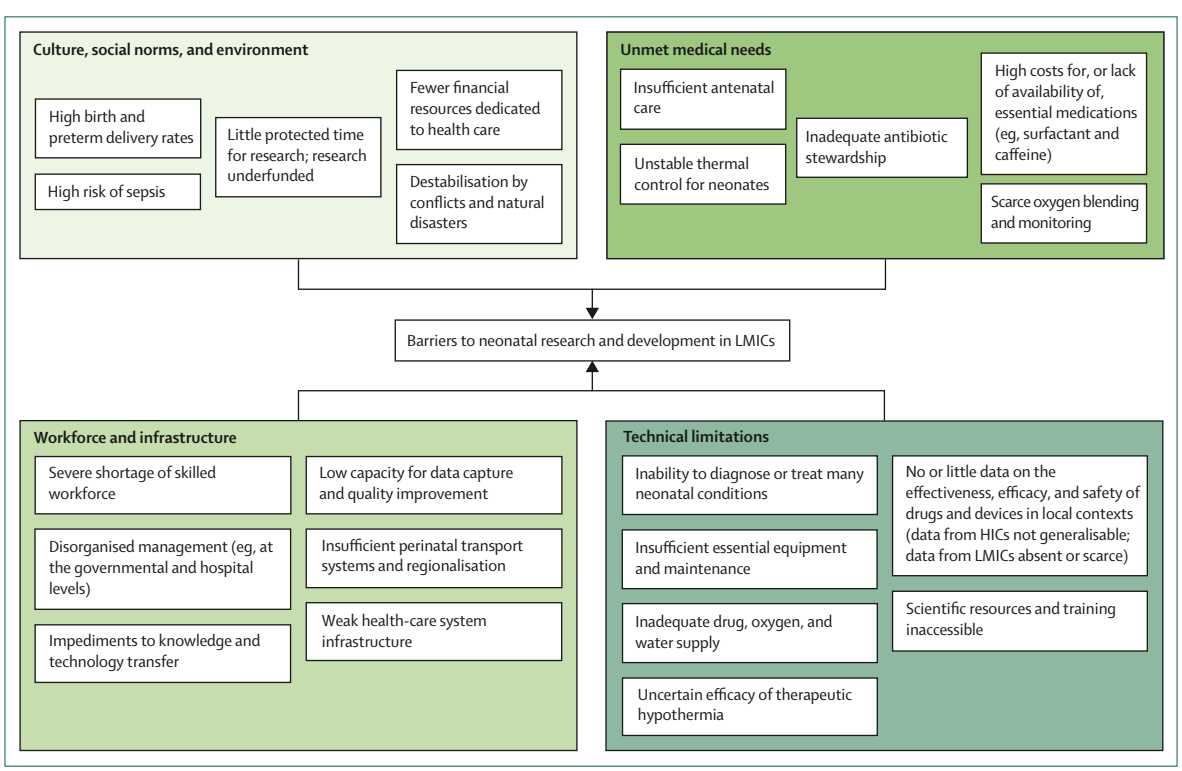

Figure 4: **Major challenges for neonatology in LMICs**
HICs=high-income countries. LMICs=low-income and middle-income countries.

anaesthesiology and perioperative medicine, obstetrics and fetal medicine, other paediatric branches, transplantation surgery, regenerative medicine, tissue engineering and artificial organs, endocrinology, genetics, and molecular biology. Many underlying principles could be applied or adapted to neonatology, and the list of lessons from obstetrics and fetal medicine and adult intensive care is extensive. Improvement of newborn health care starts with improving maternal care: in this sense, every advance in maternal–fetal medicine has also been an advance in neonatology. More recently, placental laser photocoagulation technology has helped patients with twin–twin transfusion syndrome,[135] and fetal tracheal occlusion has aided neonates with congenital diaphragmatic hernia.[136] Not all neonatal disorders can be diagnosed or treated antenatally, so collaboration between obstetricians and neonatologists is fundamental.

The same is true for the collaboration between neonatology and intensive care medicine. Mechanical ventilation was first introduced in 1962 when Huault and Thieffry[137] treated a patient with neonatal tetanus without preliminary research data or structured trial outcomes. More recently, continuous renal replacement therapy has become available to neonates, including preterm infants.[100,105] Several well known drugs from adult critical care, including pulmonary vasodilators and inotropes,[138] are also administered to neonates in life-threatening situations; however, despite strong supportive translational and preliminary clinical data, these drugs have never been formally tested in neonatal populations; there is a view that these would not be profitable due to a small market.

Cross-disciplinary partnerships might lead to good working hypotheses that lay a solid pathophysiological and pathobiological foundation for clinical trials. Collaboration between paediatric and adult medicine is also crucial because neonatal disorders often have long-term consequences, and surviving neonates are likely to require ongoing care by paediatric and adult subspecialists.

A foundation for high-quality preclinical and translational research

Mechanistic studies that provide a thorough understanding of how specific therapies work are vital and require adequate animal and translational research. These studies should also include investigation of the biological effects of sex[139] and the effects of therapeutic interventions in neonates with developing organ systems. Preclinical and translational studies are also an ideal example of cross-disciplinary collaboration with paediatric and adult critical care medicine. These studies are often easier to perform in adults because of patient size and reliable funding. With better mechanistic understanding of disorders, diagnostic biomarkers and therapeutic targets can be more readily identified. Surfactant catabolism is a typical example of discovery accumulated through these studies that might be useful in neonatology.[140–142]

Some studies of drugs or medical instruments for neonates did not account for the complexity and variety of pathophysiology[143] or involved multiple co-interventions,[144,145] which led to enrolment of infants with different pathobiology and phenotypes, despite apparently similar clinical presentations. This heterogeneity can contribute to the failure of research projects to provide consistent and useful results for implementation into personalised patient care.

Experience in other medical fields has shown the long-term benefits of preclinical models. Such preclinical models might be difficult to prioritise because they require substantial investment of time and money. An example of a high-quality perinatal preclinical project is the artificial womb with extracorporeal circulation, which seems to be promising in animal models.[146] This type of project could be groundbreaking but requires substantial long-term support to reach its aims.

Tools for precision and personalised neonatology

Medical precision requires a deep understanding of disease phenotypes and underlying mechanisms. Common neonatal disease phenotypes include bronchopulmonary dysplasia, neonatal ARDS, pulmonary hypertension, hypoxic-ischaemic encephalopathy, and necrotising enterocolitis.[138,147–150] Within each of these phenotypes, relevant subphenotypes might exist that confer greater or lesser risk of poor clinical outcomes and patients within each subphenotype might share certain biological responses to disease, which are called endotypes. The presence of heterogeneity within phenotypes can translate to considerable variability of clinical definitions, practice, and outcomes and has resulted in multiple negative clinical trials in adult and paediatric critical care.[151,152] Unlike adult medicine, the consideration of different disease pathophysiology and phenotypes has been inconsistently applied in neonatology. With more advanced understanding of mechanisms underlying multifactorial disorders and identification of patients with relevant subphenotypes that may confer higher or lower risk of poor clinical outcomes, clinical trials can adopt trial designs that leverage predictive enrichment strategies.

Neonatology lags behind adult medicine in the practice of personalised medicine,[153] in which treatment is tailored to a patient's genetic background, individual host response to critical illness, and biological characteristics, such as the presence of comorbid conditions and other clinical risk factors. Personalised neonatology must include rigorous assessments of pathophysiology, biology, developmental maturity, genotypes, and epigenetics. However, these assessments are rarely performed, owing to scarcity of research, inadequate technology, and insufficient attention from researchers, leaving neonatal care imprecise. Specific assessment of pathophysiology and biology is necessary to avoid research waste because the knowledge produced by research that ignores this will not be tailored to individual

patient needs. High-quality preclinical basic and translational research would facilitate the development of innovative interventions. This type of research must bring together neonatologists, biologists, physicists, engineers, and data scientists in collaboration, with contributions from pharmacists, veterinarians, and other professionals.

A one-size-fits-all approach to neonatology is not conducive and could possibly even be harmful to neonatal health. Flaws in several past clinical trials are at least partly a result of disregarding diverse subphenotypes and factors that contribute to variability in responsiveness within patient populations. For example, HFOV is not equally beneficial for all neonates with respiratory failure.[107] Only about 70% of infants with pulmonary hypertension respond to inhaled nitric oxide, which is partly dependent on concurrent cardiopulmonary management and their underlying conditions and pathophysiology.[138,154] Surfactant replacement therapy is guided by oxygen requirement, a crude epiphenomenon of respiratory pathophysiology.[155] Preterm infants with respiratory distress syndrome require personalised care, and, although some technologies already exist,[156] other promising technologies await further industrial development.[157] The requirement for further development risks delaying effective therapy and can in some situations result in unnecessary treatment.

Certain drugs and technologies certainly need further translational research, but not only is funding and interest from industry inadequate, but cross-disciplinary collaborations to do the research are not well established, and translational research continues to be perceived as risky and invasive. For example, the overall patient population that is eligible to receive neuroprotective drugs (eg, melatonin, erythropoietin, metformin, and allopurinol) is highly heterogeneous, so they are unlikely to be equally efficacious in every patient. They need to be tested in different animal models, mimicking the different types of brain injury, to inform clinical research.

Patients with different subphenotypes or endotypes might have better or worse outcomes (prognostic enrichment) and better or worse responses (predictive enrichment) to certain treatments. For many years, trials recruiting adults with ARDS prespecified plasma specimen collection in their protocols. This systematic sample collection enabled a combined latent class analysis of plasma biomarkers that revealed two major ARDS subphenotypes (termed hyper-inflamed and hypo-inflamed phenotypes).[158,159] Post-hoc analyses of several ARDS trials in adults subsequently showed that response to ARDS treatments differed between patients with the hyper-inflamed subphenotype and patients with the hypo-inflamed subphenotype.[160–162] Similar analyses have recently identified the same two subphenotypes in infants and children with paediatric ARDS.[163] We used data from the HARP-2 trial of simvastatin in adult ARDS164 to show that application of personalised medicine principles to future clinical trial designs, specifically ARDS subphenotyping, could halve the sample size needed to show reductions in mortality (appendix p 4).

Applying principles underlying precision medicine is directly applicable to neonatal ARDS, which has only recently been recognised as a clinical entity.[165] Future research on clinical and blood-based biomarkers of neonatal ARDS might identify similar subphenotypes with similar risk profiles. Mechanistic studies leveraging multi-omic approaches, such as RNA expression analyses, could identify patients who share similar biological mechanisms of disease and potentially similar response to treatment—otherwise known as functional endotypes. As noted by Reddy and colleagues[166] in 2020, if a biologically plausible treatment can be targeted to an endotypic mechanism, then that endotype will have revealed a treatable trait. So far, no neonatal studies have evaluated patient heterogeneity using subphenotypes or endotypes for prognostic or predictive enrichment. Small proof-of-concept studies both in preclinical models and in neonates show that endotyping might allow predictive enrichment of studies investigating respiratory consequences of prematurity.[167,168]

Better diagnostic and biomarker technology is needed to identify patients for enrolment in clinical trials and to select candidates to advance along the clinical development pathway. Advanced genomic testing, point-of-care imaging, and bioassays, either alone or in combination, are just a few of the most promising technologies that could help to characterise patient pathophysiology and biology. The US National Institutes of Health and FDA have issued specific guidelines for the development of biomarkers.[169] Nonetheless, costs and perceived burden of developing specific biomarkers to guide therapy often rule out collection of valuable biological samples from neonates. Parallel biobank development does not exist to support multicentre investigations in collecting large numbers of samples from multiple patient cohorts, which should be remedied because the ability to identify subphenotypes and to link subphenotypes to differential treatment effects would radically improve interpretation of clinical trial results.

Strengthening neonatal clinical research

It is estimated that less than 10% of health-care interventions evaluated in Cochrane reviews are supported by high-quality evidence.[170] More than two-thirds of Cochrane neonatal reviews are inconclusive because trials are too small or methodologically weak.[5,12,171] Indeed, we find that neonatology literature is expanding but with an overall tendency for original research to yield confirmatory data, pursue imprecise research questions, carry insufficient statistical power, and follow low-quality methodology. The fragility index is the number of participants in a trial whose status would have to change from a non-event to an event for the trial result to change from significant to non-significant; the higher the

number, the more statistically robust a trial might be. Across 66 trials of interventions in neonates, a median of only three events were needed to turn a significant result into something non-significant, a small number of events on which significance is concluded.[172] Triallists in neonatology have often not considered patient diversity in relation to sex, race, ethnicity, pathophysiology and pathobiology, socioeconomic diversity, and geography in the trial design, resulting in questionable generalisability of the trial data. The higher average quality of trials in adult medicine is undoubtedly linked to robust patient accrual and innovative trial designs and strategies, such as adaptive trial designs, new consent forms, real-world data,[173–175] and adherence to CONSORT guidelines. For adult patients, more tools exist to assess patient pathophysiology, identify phenotypes and endotypes, design explanatory trials, and eventually provide personalised care.

For the **CONSORT guidelines** see https://www.equator-network.org/reporting-guidelines/consort/

Best practice in neonatal care too often relies on protocols derived from expert consensus and on guidance for which there is no high-quality evidence. Strong personal beliefs and clinical bias are known to have shielded inaccurate and dangerous treatments from undergoing rigorous testing.[176] Thymic irradiation, high-dose postnatal steroids for hyaline membrane disease, and immediate cord clamping as part of active perinatal care are examples of treatments that were once widely advocated by clinicians and have now been proven useless or harmful. Meta-analyses of high-quality clinical trials revealed a reduction in neonatal mortality by 30% in babies resuscitated with air compared with pure oxygen,[177] which has led to changes in international resuscitation guidelines. For no added costs, a 30% reduction means that more than 100 000 lives per year can be saved globally by switching newborn resuscitation from pure oxygen to air.[178] These examples show how harmful practices have continued because of pervasive clinician biases and a reluctance to put fervently held beliefs to the test of randomisation.

For more on **James Lind Alliance Priority Setting Partnerships** see https://www.jla.nihr.ac.uk/

For more on the **COMET Initiative** see https://www.comet-initiative.org

Former patients and family representatives have a pivotal role in strengthening clinical research in neonatology. Parents or guardians often lack knowledge about medical therapies and have legitimate concerns about risks, but generally show eagerness to learn and spread accurate and trustworthy information. Communication and trust are absolutely essential to disseminate correct information about neonatal research and its value, especially in an era of scientific disinformation and mistrust of motives, which undermine research and medical care. When recruiting neonatal patients to studies, there is a need to accurately explain to families the disease pathobiology, clinical concerns, and existing knowledge gaps that can be addressed by the study. Former patients and family representatives' engagement could help lay people to understand the relevance of clinical trials, advocate to facilitate funding or regulatory approval, and eventually improve patient accrual in studies. Fostering trust must be bidirectional to ensure that the interventions developed are aligned with the priorities of those directly affected by the disease and that high-quality methodologies are chosen based on expert advice.

Patient and public involvement and engagement (PPIE) engages lay people who are not professionally concerned, experienced, or trained in health care and research to actively contribute to research.[179] Acceptance and understanding of PPIE in medical research differ within and between countries. Regardless of the requirements of funders, sponsors, or regulators, neonatologists should take the initiative in involving former patients and family representatives in advisory roles for neonatal clinical studies.

Organisations dedicated to increasing neonatal PPIE activities are already providing a voice for children and families at continental, national, and regional levels.[180] For example, James Lind Alliance Priority Setting Partnerships have involved non-expert perspectives in identifying priorities to be addressed in preterm birth research. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative has developed a handbook to guide researchers on PPIE. The UK Nuffield Council on Bioethics advises researchers in relation to PPIE.[181] Importantly, opinions might be considerably different between former NICU patients and relatives of current patients. As we are starting to have the possibility to consult directly with NICU survivors, this difference in perspective should also be considered, and direct patient representation should be prioritised whenever possible and appropriate.[182]

The importance of high-quality clinical trial design

High-quality trial design is crucial in neonatal research because interventions at this age can induce long-term effects on the developing brain and other organs.

In 2009, Chalmers and Glasziou[183] estimated that more than 85% of the billions of US dollars invested in biomedical research each year did not lead to sufficiently new data or insights into disease course or care. Of their 17 recommendations for increasing value and reducing waste by improving prioritisation, design, conduct, analysis, and reporting of clinical research, as well as regulation and management,[184,185] 12 recommendations place primary responsibility for increasing value and reducing waste on funders, regulators, policy makers, health-care system managers, sponsors, ethics committees, publishers, and legislators. It is therefore important that neonatologists and other medical specialists, parents, and former patients engage in high-level partnerships with these stakeholders to enhance the successful completion of research studies.

Clinical trials often have several limitations (usually inter-related), such as insufficient sample size, no patient phenotyping, missing data on pharmacokinetics and

pharmacodynamics to support correct choice of dose, insufficient knowledge of disease mechanisms, non-standardisation of background care and co-interventions, site variability regarding enrolment or care, loss of equipoise, and fundamental issues in study design, implementation, data entry, and analysis. The problem of sample size is crucial because the effect size cannot always be large, and therefore potential clinically relevant benefits might go unnoticed. These limitations often result from overestimating the number of eligible patients, poor consent rates, and loss of equipoise over time. A randomised controlled trial might not always be possible, feasible, and ethical or have the best design: this is more likely to be the case for rare conditions and, notably, in perinatology, critical care, and resuscitation.[186–188]

Certain principles of scientific rigour are readily applicable to neonatology. For example, after multiple disappointing clinical trials of candidate therapeutics for adult stroke, the adult stroke community came together through the Stroke Treatment Academic Industry Roundtable to focus on the need for greater rigour in the conduct, reporting, and analysis of animal and clinical studies to improve innovation from bench to bedside.[189] In neonatology, former patients and family representatives have noted that current research often focuses on researchers' own perceived needs rather than issues that actually matter most to them, highlighting how to improve the outcome choice.[190]

Enhancing research culture and training in neonatology

Neonatology is not formally recognised as a medical specialty worldwide. Where neonatology curricula exist, clinical research training is often omitted. Obstacles to high-impact clinical research include insecure career pathways for academic and non-academic researchers, prohibitively competitive public sector funding schemes, difficulties in conducting multinational studies, and the commercial perspectives of the corporate sector. Public sector health systems tend to hold clinical academics in high regard, and career development pathways are funded to secure a sustainable workforce. By contrast, commercially driven health-care systems view clinical research as an inferior career pathway, with poor pay and esteem. Hard-pressed health-care systems are often forced to prioritise routine patient care to the detriment of research and innovation. Furthermore, public health sector clinicians in low-resource settings do not have sufficient protected time for research.

Research networks can help to improve patient recruitment rates and trial quality.[191] There are many examples of effective research networks for greater engagement of neonatologists within established programmes, such as the US National Institute for Child Health and Development Neonatal Research Network, Canadian Neonatal Network, US Extracorporeal Life Support Organization (ELSO), European ELSO, Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, Pediatric Pulmonary Hypertension Network, BPD Collaborative, transatlantic Surviving Sepsis Campaign, European Society of Paediatric and Neonatal Intensive Care (ESPNIC) scientific sections and working groups, UK Neonatal Collaborative, and UK National Institute for Health and Care Research networks. Improvements in research literacy among neonatologists and allied health professionals, greater emphasis on multidisciplinary, cross-sector collaboration, and participation in these networks would be helpful to improve neonatal care. Additionally, professional societies and training bodies have an important role in promoting clinical research as an essential component of good patient care. Equity requires that every sick neonate with a condition that does not have an evidence-based standard of care is offered at least one clinical trial.

For the **European Society of Paediatric and Neonatal Intensive Care (ESPNIC) scientific sections and working groups** see https://www.espnic.eu/science/scientific-sections/

Elevating the quality of real-world and observational studies

The growing availability of high-quality, real-world observational data, especially when coupled with technologies for large-scale data management and the application of powerful causal inference analytics, offers potential approaches to acquire high-quality evidence without having to do a clinical trial.[175] Other opportunities to enhance evidence-based newborn care include multi-arm, multistage trials, adaptive designs, registry trials, and other novel approaches that were used successfully during the COVID-19 pandemic to quickly build an evidence base.[175] Widespread adoption of the electronic medical record provides unprecedented opportunities to improve care through analysis of large datasets in audits, observational studies, and comparative effectiveness studies. Sophisticated search functions can identify relevant research cohorts, and efficient and cost-effective mechanisms now exist to extract, link, and analyse large amounts of data. Adult medicine has shown that leveraging these data is possible and often useful. Large datasets, free from selection bias, not only reduce the research burden but might also enable higher-powered, lower-risk studies and increased confidence in research outcomes.

Many jurisdictions permit use of retrospective de-identified health information for quality improvement initiatives with a waiver of consent. For added transparency, institutions might issue a generalised statement or notification to families upon hospital admission, highlighting how health information can be used for health research. This approach to integrating participants as partners in research governance and operations seems to have broad acceptance by study participants.[192] Given the accessibility of large amounts of personal information and increasing potential for sophisticated research tools to be incorporated within the electronic medical record, careful consideration must be given to privacy and confidentiality without increasing the administrative burden and compromising research feasibility. Non-specific ongoing

consent (also known as broad permission) or opt-out consent are good alternatives to traditional prospective informed consent. However, these types of consent could lead to bias if a high proportion of families wish to be excluded from the dataset. In this regard, digitally linked routine records that collect parent-reported follow-up data once infants are discharged from the NICU is a particularly promising innovation.[193]

The UK National Neonatal Research Database is a tangible example of how digital tools can elevate study quality.[194] This database has complete representation from all neonatal units in the UK. With strong parent and patient support, the National Neonatal Research Database sees less than 1% of parents choosing to opt-out of the inclusion of their child's data.[194] The data are a standardised extract from electronic patient records and are available as a national and an international resource to external researchers. The database supports a wide range of study types, including randomised controlled trials and observational research, as well as audits, surveillance, and quality improvement programmes. Such databases can become very useful tools to more precisely define medication use, dose, safety, and efficacy for well phenotyped patient cohorts, providing real-world data that will contribute to drug development.

Defining clinical outcomes

Age-specific clinical outcomes of interest need to be defined better for neonatal disorders. Clinical researchers in the UK recently proposed core outcome sets for neonatal research[195] and for maternal and neonatal research during major disease outbreaks.[196] Similarly, an international core outcome set has been developed for treatment trials in necrotising enterocolitis.[197] Meaningful outcome definitions are often not optimised without sufficient engagement between investigators and families.[198] For example, neurodevelopmental impairment causes concern for both clinicians and families but can be defined in many ways. A deeper understanding of the risks of long-term cognitive and motor impairments is important to guide conversations with families, particularly those conversations involving shared decision making in critical neonatal situations.[199] Neurodevelopmental impairment is most commonly defined in terms of academic performance, executive functioning, language ability, and phenotypes such as autism and attention deficit hyperactivity.[200–203] Few data are available about neurocognitive outcomes in adulthood,[203] but some evidence suggests that adults who were born very preterm display structural and functional brain alterations[204] and have adverse cognitive, socio-emotional, and behavioural outcomes[205] affecting social relationships and academic and economic attainments.[206] Future studies should include assessment of mental health and psychiatric profiles beyond diagnostic boundaries and strive to accommodate both the presence of complex comorbidities and subthreshold symptoms. This requires funders to acknowledge the importance of long-term follow-up and multidisciplinary collaboration to establish shared infrastructure for long-term surveillance.[207]

The use of AI and deep-learning approaches promises to revolutionise the task of predicting outcomes during the neonatal unit stay. Feng and colleagues[208] found that the use of a novel deep learning survival risk monitor for preterm infants more accurately predicted mortality than other approaches, including the Clinical Risk Index for Babies II score. Finally, after clinical research is completed, the challenge to rapidly translate good research into practice remains.

Overall recommendations

There is an urgent need to catalyse innovation through all the challenges, constraints, and opportunities. We propose specific actions to strengthen bench-to-bedside research in neonatology by mobilising stakeholders and by instigating commitment from and collaboration between neonatologists and the following stakeholder groups: research ethics committees and regulatory agencies; industry; physicians and allied health-care professionals; governments, universities, and academic medical centres; and former patients or family representatives and advocacy groups. We acknowledge that the specific actions within each recommendation will be shaped by local resources; regardless, the recommendations to each stakeholder group are complementary, inter-connected, and unanimously targeted towards improving neonatal health, with a central role of the neonatologist in guiding neonatal care and research (figure 5).

Recommendations for research ethics committees and regulatory agencies

Merely increasing research funding for neonatology research will not spur drug and device development in the current regulatory environment.[209] Research ethics committees and regulatory agencies are important in the context of generating high-quality evidence for treating neonates. For example, some regulatory agencies have started communicating with each other to render regulatory standards and guidance to clinical investigators and industry more consistent.[210] National research ethics services have been established in numerous countries, obviating the requirement to seek ethics approval from every hospital or facility individually. Despite these developments, excessively precautionary mindsets, miscommunication among investigators, research ethics committees and regulatory agencies, insufficient numbers of neonatologists to evaluate research projects, and inadequate tools and procedures for undertaking neonatal research act as barriers to innovation. Mechanisms to facilitate approval of trials across jurisdictions such as the EU and speed up the associated administrative processes are urgently required and would enhance the rate of progress of neonatal care.

Barriers encountered by research ethics committees and regulatory agencies in neonatology include bureaucracy, inconsistencies in priorities underlying regulatory decision making between authorities, privacy issues preventing data collection and sharing, use of generic pharmacological criteria for medical device technologies, uninformed considerations of neonatal clinical reality and lack of neonatologist expertise, rigidity in neonatal research and clinical processes, insufficient support from regulatory agencies for industry to undertake neonatal research, and a misperception that research and development projects in neonatology are not important. Solutions to these barriers are shared in panel 5.

Recommendation 1: recognise that neonates have a right to care that has been assured through research

The ethics and regulation of research practice are safeguards for our patients and critical determinants for the development of novel therapies, but, to be successful, the right to improve newborn care through research must be fully recognised. It was once considered unethical for children to be involved in any research that was not of direct benefit to them. This viewpoint, based on the notion that the cardinal role of research regulators was to protect children, as vulnerable minors, against the dangers of research was successfully challenged by the British Paediatric Association, the forerunner of the UK Royal College of Paediatrics and Child Health, in 1980. It pointed out that to focus solely on protection was to deny children the right to benefit from research and have their care assured through research. As concepts developed, the Royal College of Paediatrics and Child Health issued updated research ethics guidance.[211] Unfortunately, this major conceptual shift has not yet been implemented by all research ethics and regulatory bodies worldwide. The recently amended Declaration of Helsinki now also notes that under-represented groups have the right to participate in medical research.[212]

Recommendation 2: improve communication between research ethics committees and regulatory agencies

More crosstalk between regulatory agencies and research ethics committees and more active listening to the perspectives of neonatologists and families is required. For example, when a trial is approved by a given agency, that approval should be automatically considered valid by other ethics committees and regulatory agencies if sufficient commonalities exist, or at least used to facilitate and shorten the approval process. Appropriate agreements between agencies and governments need to be in place to facilitate the research and development process. With the rare exception of genetic variations, the main neonatal disorders are the same in every country, and therefore incongruence is unacceptable.

This recommendation is directed to research ethics committees, the EMA, and the FDA, as well as other national bodies, such as the UK Medicine and Healthcare Regulatory Agency, the Australian Therapeutic Goods Administration, and the Japanese Pharmaceuticals and Medical Device Agency. Collaboration between agencies and research ethics committees or other regulatory bodies will not only shorten the time needed to start neonatal research and development projects, but also has additional benefits derived from shared clinical and pathophysiology knowledge. Multinational collaboration might help by expanding the area in which an innovative drug or device can be tested and used, thereby stoking the interest of industry, which often sees neonatology as a small market that is unworthy of investment.

This recommendation can be fulfilled by organising regular meetings of the FDA, EMA, and other regulatory agencies focused on the needs of neonates. Moreover, investigators must be provided with an adequate procedure to appeal against decisions of regulatory agencies, and the rebuttal should be considered in a fair and transparent matter.

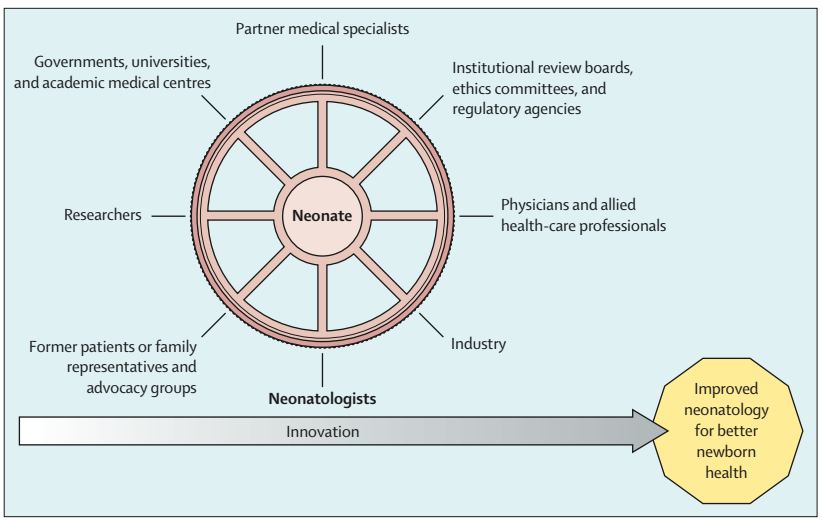

Figure 5: **Stakeholder collaboration for innovation in neonatology and to achieve better outcomes for neonates**

Recommendations were developed for each group of stakeholders that are complementary and interconnected, and tasks are best shared among different actors. The wheel and spokes connecting every stakeholder illustrates how they work together and how their actions might be influenced by the recommendations in a shared way. Each problem can be addressed in different ways by the various stakeholders, with the central role of neonatologists as medical leaders in neonatology practice. The common goal is to improve neonatal health.

Recommendation 3: develop flexible consent approaches for neonatal research

A key tenet of participation in clinical trials and other research is the concept of informed consent. Consent should be voluntary, informed, specific, and current. Explicit prospective consent avoids confusion, aids transparency, and maintains trust in the research process. In neonatal medicine, potential participants cannot provide informed consent themselves, and consent is sought from a legally authorised representative, usually the parent or legal guardian.

Panel 5: **Solutions to barriers encountered by institutional review boards, ethics committees, and regulatory agencies**

Excessive bureaucracy
- Establish relationships and facilitate streamlined communication between regulatory agencies
- Introduce a single institutional review board for multicentre trials

Discrepancies between authorities
- Recognise decisions of other institutional review boards and regulatory agencies
- Create short, simple application processes and forms
- Create short summaries for parental consent forms
- Use creative tools to explain forms (eg, videos and AI)
- Use alternative forms of consent (eg, waived and deferred, non-written, and opt-out consent)
- Use data linkage tools
- Ensure fair, transparent, and informed rebuttal processes
- Adopt a mindset that prioritises patients' best interests rather than patient protection

Privacy issues preventing data collection and sharing
- Lessen data collection and sharing requirements (eg, use pseudonymised data)
- Classify projects according to privacy risk
- Adopt a mindset that prioritises patients' best interests rather than patient protection

Use of generic pharmacological criteria for medical device technologies
- Recognise different features of medical device and drug development
- Establish dedicated pathways for medical devices
- Avoid over-precautionary policies when classifying medical devices

Uninformed considerations of neonatal clinical reality and lack of neonatologist expertise
- Avoid blocking research of unapproved therapies that are standard of care because this is unethical and dangerous
- Allow recruitment of neonates in clinical studies by default
- Expand paediatric investigational plan model to include neonates
- Consult with key opinion leaders with expertise in neonatology, and invite neonatologists to review projects, leaving secondary roles to physicians who are not specialised in neonatology
- Adopt a mindset that prioritises patients' best interests rather than patient protection

Rigidity in neonatal research and clinical processes, originally designed for adult medicine
- Consider novel trial designs and methodological approaches (eg, platform trials, pragmatic trials, machine learning, adaptive trials, Bayesian methods, and real-world data)
- Subdivide applications according to risk stratification
- Allow conditional marketing authorisation to include neonatology, or at least some neonatal disorders (eg, bronchopulmonary dysplasia and necrotising enterocolitis), in the orphan designation space
- Consult with key opinion leaders who are neonatologists and have neonatologists as project reviewer, leaving only secondary roles to physicians not specialised in neonatology

Insufficient support for industry
- Incentivise industry by extending exclusivity or orphan designations
- Develop specific guidelines for neonatal research and development
- Support and help industry in study designs

Perception of research and development projects for newborn health as unimportant
- Start specific training in neonatology for institutional review board and regulatory agency members
- Adopt a mindset that prioritises patients' best interests rather than patient protection
- Consult with key opinion leaders in neonatology rather than with other specialists

This process can be straightforward for some clinical trials with neonates, but critical situations might render prospective consent impossible, and several factors can render prospective informed consent impracticable. Obtaining prospective informed consent for newborn resuscitation research or trials of emergency interventions, for example, is challenging. Approaching parents or guardians when they are under psychological stress, in pain, or under the effects of strong medications might be ethically unacceptable. Innovation in the research consent process for clinical trials to ensure equity for newborn infants has therefore received particular consideration. Alternative forms of consent must be considered to ensure that clinical trials are feasible, generalisable, free from selection bias, and place the best interest of the patient foremost.

In 2008, the UK Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations[213] announced that children aged 0–17 years could enrol in trials before informed consent if this was warranted by the urgency of the situation. The most recent edition of the Declaration of Helsinki[212] outlines the specific circumstances in which study enrolment can proceed even if no legally authorised representative is available and the research cannot be delayed. These circumstances are, first, specific reasons for involving participants with a condition that renders them unable to give informed consent have been stated in the research protocol; second, the research has been approved by a research ethics committee; and, third, free and informed consent to remain in the research will be obtained as soon as possible from a legally authorised representative.

These principles can be applied to the neonatal unit and the delivery room. Research in these challenging settings or with neonates is not impossible; however, eligibility is unpredictable: extremely preterm births represent 0·67% of livebirths but 45% of infant deaths.[214] In countries where conditions such as pre-eclampsia can be treated in advance of birth, there might be time for meaningful discussion and prospective consent. In high-resource settings, these infants are likely to be born in a facility equipped with medications such as antenatal steroids and magnesium sulphate to manage infants at high risk to improve short-term and long-term outcomes. By contrast, high-risk deliveries with rapid onset, such as those precipitated by placental abruption, occur before prospective consent can be obtained. These neonates are the most vulnerable, but stand to benefit the most from participating in and contributing to research. However, they are often excluded because of stringent consent requirements.

Ideally, the sample of patients recruited to a clinical trial should be representative of the population to which the results will be applied. The SUPPORT trial showed the effect of prospective (antenatal) consent requirements on the representativeness of the study sample.[215] Infants enrolled in the trial were more likely to have been exposed to prenatal steroids and intubation in the delivery room than those who were eligible for the trial but not enrolled. Unsurprisingly, enrolled infants had lower rates of poor outcomes. Whether inclusion of a higher proportion of eligible infants would have altered the conclusions of the trial is unclear. A welcome advance is that the UK Health Research Authority now accepts explicit mention of an "inclusion benefit" in patient information sheets,[216] referring to how patients recruited to clinical trials frequently fare better than those who do not participate, regardless of the intervention to which they are randomly assigned.

Alternative forms of consent processes have been considered and proposed, including waiver of consent, opt-out consent, and deferred consent (also termed research without previous consent).[217,218] Some of these have been used in adult critical care in situations in which patients cannot communicate, mirroring a common scenario in neonatology and paediatrics.[219] Their benefits and burdens must be balanced—ie, the maintenance of patient dignity and research integrity should be sufficient to outweigh the principle of autonomy.[219] Several neonatal trials have been conducted without prospective written informed consent.

Evidence suggests that deferred consent is acceptable to families, especially if the intervention in question is already in practice.[220] However, concerns remain that deferred consent can act as a subtle form of coercion that removes parental rights, given that families might be more likely to give consent after the intervention has been performed.[221] Trust in the research process is particularly eroded by serious adverse events or deaths associated with the intervention. Although deferred consent overcomes some ethical challenges, others are created. Deferred consent should be obtained as soon as this option is considered reasonable, but it creates, at least in the EU, privacy problems regarding data access before consent is granted. In some situations, deferred consent is not feasible (eg, when a family ends contact with the hospital following the death of their child). These events should be anticipated with an appropriate management plan that sensitively respects family wishes while maintaining research integrity. To prevent the possible introduction of biases, consideration should be given to prospectively gaining a waiver of consent for the use of anonymised minimal datasets that capture at least the main outcomes.

Recommendation 4: focus on optimising outcomes and patients' best interests

Ethics boards and regulatory agencies must weigh the risks associated with a new intervention against the risks of maintaining the status quo. Rejecting an innovative drug or device might be a missed opportunity to improve outcomes for neonates; indeed, recent experiences across neonatology shows how over-caution can be detrimental to newborn health.

Ethics boards and regulatory agencies should not inhibit research involving off-label drugs and devices that are already considered to be standard care in real-world practice. This unethical policy is a threat to newborn health. Notable examples include the use of HFOV as rescue ventilation and surfactant for neonatal ARDS.[222,223]

Institutional ethics boards in France are called *Comités pour la Protection des Personnes,* which translates into People Protection Committees. The suggestion that ethics boards must protect humans from physicians, nurses, and new drugs and devices fosters an unfair and unhelpful view that treating a disease using existing drug and device technology is more ethical than testing new solutions under rigorous, closely monitored research pathways. One should not assume that available diagnostics and therapeutics would exist had the same precautionary philosophy been applied to their research and development.

We have witnessed neonatal trials rejected and approved by different institutional review boards, or trials rejected after only administrative amendments (ie, no scientific changes) despite their original approval. This is unethical and dangerous for newborn health. A culture change is necessary and possible. Proportionate risk assessment should be applied to clinical research with neonates, replacing the previous blanket high-risk categorisation of all neonatal studies. In proportionate risk assessments, ethics boards and regulatory agencies should trust the evaluation of study feasibility and acceptability made by neonatologists and families. A European initiative is examining proportionate risk approaches in clinical trials; its work on tailoring the

control measures to a grading of patient risks serves as a good example of innovation.[224]

The COVID-19 pandemic stimulated innovation in clinical research during emergency situations, and some of that innovation could be applied in neonatology. New regulatory approaches included facilitated application submission and peer review processes. The EMA initiated a rapid procedure through which a PIP for COVID-19 treatments or vaccines could be agreed within 20 days compared with the usual 120-day timeframe.

The best interests of patients are served if research ethics boards and regulatory agencies ensure lean, consistent, and expeditious application processes characterised by short turnaround times and a proactive attitude to accelerating the research process. Blocking the research process for technicalities does not serve patients' best interests. Simplified application processes should be harmonised across countries, and steps already completed in one country should be acceptable in another.

It is important that research ethics boards and regulatory agencies recognise the features of medical device research in order to facilitate its development, although dedicated and simplified regulatory pathways for neonatal devices are required. Current medical device regulations are overly cautious and do not distinguish between devices and their associated risks; for example, the risk profiles differ between interventional versus non-interventional devices and between invasive versus non-invasive devices. We recommend data monitoring and classification systems to age label devices in paediatric subpopulations and facilitate the approval of devices that are already authorised in other paediatric subgroups.

Recommendation 5: include neonates in research projects by default and exclude them only with clear scientific justification

Including neonates in research projects and drug development programmes as the default approach should be the norm unless there are clear, strong, and specific concerns that justify their exclusion.[225] Cases for which there is a strong justification to exclude neonates from enrolment are rare, and regulatory bodies should be made aware of these cases.

Regulators and pharmaceutical companies often agree to exclude neonates from PIPs because they fear increased risks and the population is often small. These concerns stem, in part, from issues in understanding differences in disease pathobiology, developmental issues, and a scarcity of pharmacokinetics and pharmacodynamics data. More translational research is needed to increase our understanding of these issues.

Recommendation 6: recognise the need for specific neonatal expertise in all stages of neonatal research and development

According to the Declaration of Helsinki, medical research should be conducted only by individuals with appropriate education, training, and qualifications and supervised by a competent and appropriately qualified physician.[212] This corresponds to a neonatologist in neonatology, which is why all countries should recognise the field of neonatology and dedicate resources to building this formal expertise.

Bidirectional training and exchange among ethics boards, regulatory agencies, and neonatologists are crucial to enable a more dynamic and efficient environment for translation of research into effective innovation. Neonatologists must assume a leading role in this interaction, representing the voice of the neonatal medical community, while other specialists and health-care professionals can advise on specific topics. This would improve engagement of regulators with the neonatology community and facilitate the creation of advisory panels specifically for neonatal issues.

***Panel 6:* Solutions to barriers encountered by industry**

Insufficient cross-disciplinary collaboration

- Remain open to cross-disciplinary collaboration
- Use preclinical and translational data from projects on diseases with similar biological and pathophysiological features
- Collaborate with key opinion leaders in neonatology in clinical pharmacology studies

Insufficient funding

- Consider industry–public partnerships
- Consider industry–philanthropy partnerships

Precautionary mindset

- Revise internal compliance directives in agreement with neonatologists
- Identify priorities through discussion with key opinion leaders in neonatology
- Introduce compliance agents to real-world problems faced in neonatal critical care

Lengthy and high-risk research and development pathways

- Support preclinical and translational research to understand the mechanisms of neonatal disease and inform research and development decisions
- Consider neonatology (or at least some neonatal disorders) as orphan areas
- Prioritise clinical studies on repurposed drugs through discussion with key opinion leaders in neonatology
- Prioritise clinical studies with solid pathophysiology and pathobiology data
- Do not engage in projects without solid pathobiology and pathophysiology preliminary data, although they might look appealing from a marketing point of view
- Consult with key opinion leaders in neonatology

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Recommendation 7: create drug development plans specific to neonates

Several strategies for creating drug development plans specific to neonates are possible, and they are not mutually exclusive. EU and US regulations require sponsors to follow PIP processes for new drugs, a step in the right direction, but the concept should be expanded to include specific processes for neonates, as very few of these plans currently do. To facilitate the process, it might be helpful to develop specific plans that can be shared between regulatory agencies, with targeted questions that are specific to neonates. An exclusivity extension could help towards incentivising industry to invest in neonatal research and development. Another strategy would be to include neonatology, or at least some neonatal disorders (eg, bronchopulmonary dysplasia and necrotising enterocolitis) in the orphan designation space to facilitate the related research and development.

Recommendations for industry

Partnerships between industries and academia have too often been unproductive, and the perception of neonatology as a small and inconsequential area of opportunity is a barrier to innovation in neonatology. Barriers encountered by industry include insufficient cross-disciplinary collaboration, insufficient funding, a precautionary mindset, and lengthy and high-risk research and development pathways. Solutions to these barriers are summarised in panel 6.

Recommendation 1: support preclinical and translational research grounded in a basic understanding of pathobiology and pathophysiology

Industry mostly funds clinical studies. Yet discovery and development of innovative mechanistic approaches with promising therapies and a high likelihood of clinical benefit could be enhanced with more support and comprehensive collaborations at earlier stages of basic and translational research. Industry should support collaborative clinical pharmacology studies and basic studies on developmental biology, pathophysiology, and pathobiology of neonatal diseases to better understand their mechanisms, inform further research, and help in understanding which disease mechanism to target. Industrial research and development projects that are not grounded in reliable pathophysiology and pathobiology are quickly abandoned or not started, even though they might seem theoretically appealing from a marketing perspective. Therefore, engagement with academic researchers at earlier stages of research could reduce the likelihood of failure, saving years of research, industry money, and resources.

Similarly, industry should expand collaborations with academic investigators to conduct pharmacokinetic, pharmacodynamic, and dose-finding studies, while beginning to assess the impact on key endpoints for larger and more rigorous studies to follow. The expansion to non-industrial partners might save time and resources and could lead to a better understanding of clinical unmet needs for future markets.

From a practical point of view, these approaches can be exemplified by multidisciplinary and interdisciplinary collaborations between clinicians and scientists from different fields that share biological and pathophysiological similarities. This strategy might further translate into optimising the use of models, tools, reagents, and data obtained from different projects, which might eventually overcome old boundaries between researchers within the same industry or with those working in the academic field and even in different specialties.

Recommendation 2: establish novel funding models and collaborate with other funders

Collaboration is necessary for a new drug or device to succeed through the research and development pathway and to accelerate subsequent review by regulatory boards. The burden of this should not be exclusively on industry; industrial–academic collaborations are pivotal and require early and regular communication. When the allocated funds from industry and the academic institution are not sufficient to develop a new intervention, alternative funding sources can come from private–public partnerships, collaborations with philanthropic groups, crowdfunding platforms, and charities. These alternatives are also suitable to support research in academic and hospital (both preclinical and clinical) settings. The quest for novel funding models should include public funders, such as the US National Institutes of Health, the European Commission, or equivalent bodies at national and regional levels. Advocacy for the importance of neonatal research and development should come from all stakeholders, stressing the principles of value-based neonatology and the returns on investment for the whole population and future generations.

Recommendation 3: simplify internal compliance procedures and avoid barriers to neonatal research and development

Industry must quickly and radically revise and simplify internal legal and compliance policies, seeking advice from key opinion leaders in neonatology. Industry policies tend to be risk averse and extremely precautionary, with barriers added to those of ethical boards and regulatory agencies, which do not serve the interests of patients or industry. This recommendation aligns with our recommendation to ethical bodies and regulatory agencies—that compliance procedures should consider the interests of industry, patients, and society more broadly, rather than only focus on unknown or theoretical risks.

Risks should always be evaluated by considering the clinical situation together with neonatologists and families, and not only from an administrative point of view. Regular communication between neonatologists and industry is crucial. A less cautious approach might improve patient outcomes and foster fruitful industrial and commercial opportunities, and neonatologists should be central advisers in the design of internal compliance procedures and evaluation of research and development projects.

Recommendation 4: accelerate and improve the research and development pathway

Industry has an important role in addressing impediments to shortening the research and development process. Although shortcuts might improve the timeline to approval, they leave doubts about safety. Progress can only be accelerated responsibly by choosing the right priorities—eg, by removing unnecessary bureaucratic steps, strengthening early preclinical studies and early translational pilot investigations, and collaborating closely with neonatologists.

The concept of considering some neonatal disorders in the category of orphan diseases should be strongly supported by industry. Research into neonatal diseases such as bronchopulmonary dysplasia, necrotising enterocolitis, and life-threatening malformation might also inform therapeutic strategies for other conditions, including those affecting adults. Investigations of repurposed drugs should also be prioritised because the pathway can be considerably shorter than for new drugs.

Recommendations for physicians and allied health-care professionals

Barriers to innovation in neonatology are also encountered by physicians and allied health-care professionals, such as insufficient cross-disciplinary collaboration, inadequate resources and tools for preclinical research, inappropriate clinical outcome choices, inadequate clinical study design and analysis, inadequate research expertise and training, and public distrust and undervaluing of medical leadership. Solutions to these barriers are presented in panel 7.

Recommendation 1: demand, develop, and support high-quality standards for preclinical and clinical research in neonatology

Medical research evolves rapidly as new methodologies for both preclinical and clinical research develop. Therefore, physicians and allied health-care professionals involved in neonatal research need to be more rigorous and methodical by conducting adequate basic, translational, and clinical pharmacological studies before observational studies and hypothesis-driven large clinical trials. Following these preclinical studies, clinical trial design should be informed by pathobiology and principles of personalised neonatology that leverage predictive and prognostic enrichment strategies. For example, statistical analytics have become more refined and advanced, new tools to assess patient pathophysiology and biology functions are available to identify signalling pathways, and we have reliable standards to report research findings. These high standards and up-to-date methods should be applied to neonatal research to achieve the level of scientific rigour and quality seen in other medical specialties.

Recommendation 2: move out of silos and actively collaborate with researchers from diverse medical specialties

Neonatology is often seen as separated from the other medical specialties. This tunnel vision is dangerous. The unique physiological and biological characteristics of neonates should not prevent us from leveraging knowledge, tools, and experience accumulated in adult and paediatric medicine, with adaptations, as needed. Collaboration through trans-generational (ie, people working on neonatal diseases and those working on adult consequences) and cross-disciplinary working groups is also needed with biologists (especially developmental biologists), biomedical engineers, physicists, pharmacologists, informatics and data scientists, statisticians, and social scientists. For example, preclinical organoid research, in silico models, and omics sciences that are progressing paediatric and adult disease research should be adapted and applied to the problems of neonates.

Recommendation 3: embrace smarter clinical research towards more personalised neonatology

Smart clinical research is cost-effective, statistically efficient, methodologically robust, and builds on individual patient pathophysiology and biology. Neonatologists should use new data collection techniques (eg, miniaturised imaging and point-of-care tools allowing phenotyping, endotyping, and biobanking), analysis tools (eg, big data analysis and AI), and local registries for rare diseases. Electronic patient files provide real-world data for high-quality observational studies. Personalised neonatology is now possible because many technologies are non-invasive, minimally invasive, or require minimal sample collection. To harness promising opportunities, smart research should also facilitate multidisciplinary collaborations across the whole pathway of discovery, from preclinical innovation to the translation to clinical care.

Recommendation 4: promote early clinical pharmacology studies

Drug research and translation of pharmacological therapies to clinical care require pharmacokinetic and pharmacodynamic assessments. Adequate preliminary clinical pharmacology studies are needed and require early input from clinical pharmacologists at the design phase. Microassays allow pharmacokinetic and pharmacodynamic studies on small amounts of biological fluids, overcoming technical, methodological and

Panel 7: **Solutions to barriers encountered by physicians and allied health-care professionals**

Insufficient cross-disciplinary collaboration
- Lead multidisciplinary working groups with other specialists involved in neonatal care such as obstetricians, fetal medicine experts, paediatric surgeons, paediatric cardiologists, and geneticists
- Collaborate with adult critical care, paediatric subspecialties, basic science departments, and translational researchers across biotechnology, IT, and the social sciences
- Organise trans-generational (ie, people working on neonatal diseases and those working on adult consequences) and cross-disciplinary workshops and working groups
- Use developmentally appropriate disease models modified from other settings

Inadequate resources and tools for preclinical research
- Share preclinical facilities and tools with other specialties
- Use integrative physiology and developmental biology tools
- Use new disease models (eg, organoids and in silico models), omics science, and microassay technology
- Use high-quality research methodology and advanced statistical analysis tools

Inadequate clinical study design and analysis
- Conduct adequate preliminary basic and translational studies for high-quality clinical research based on principles of personalised neonatology
- Aim for large multicentre trials over small single-centre trials
- Avoid research waste
- Include adequate clinical pharmacology with pharmacokinetic, pharmacodynamic, and dose-finding studies
- Use registries, electronic health records, and data fusion resources
- Use big data analysis, machine learning, and AI
- Standardise tools across sites that are specifically dedicated to neonates
- Establish internal databases of clinical data connected with electronic patient files
- Investigate repurposed drugs
- Develop manuals of operations describing standards of care across multiple sites

Inappropriate clinical outcome choices
- Connect with experienced clinical colleagues
- Engage in bidirectional conversations with parents and former patients
- Use preliminary trans-generational databases and linkage (including health economic data)
- Only target meaningful outcomes with well established and pathophysiologically solid endpoints

Inadequate research expertise and training
- Create international networks with expert researchers from various disciplines and professions to supervise
- Harmonise protocols and tools among researchers
- Advocate to recognise neonatology as a medical specialty and to have leading neonatologists as professors
- Advocate to increase research training
- Advocate for simpler procedures
- Establish simpler internal procedures (universities and hospitals) for neonatal research

Public distrust and undervalued medical leadership
- Address public perceptions of research, highlighting the value of scientific knowledge and competence
- Improve communication of technically difficult information to non-experts and fight misinformation with reliable scientific sources
- Act as patient advocates and coordinators of the whole health-care team
- Be coordinators and main assessors of neonatal research projects
- Lobby with governments and other stakeholders for official recognition of neonatology as a discipline and for neonatal research and development as a public need
- Create clear pathways to academic neonatology and training in neonatal research and development

ethical challenges. This area has been neglected in neonatology but its use is warranted given the distinctiveness of neonates in terms of drug metabolism and elimination and the effect of gestational age on these functions.

Recommendation 5: target meaningful outcomes with well established pathologically and physiologically solid endpoints

Meaningful outcomes (particularly for rare diseases and life-threatening malformations) are derived from bidirectional discussion between neonatologists, other medical specialists, nurses, translational scientists (eg, biologists, physicists, and pharmacologists), former patients and family representatives, and industry. The choice of an outcome should be reasonable, based on previous research data, and relevant to patients and their families.

Bidirectional discussions should not only serve to inform the choice of outcomes but also serve to educate lay people (eg, former patients and family representatives) and return research results to families and caregivers. The choice of outcomes should not only be optimised but also harmonised to facilitate comparison between research projects and incorporation of individual study findings in meta-analyses.

Recommendation 6: reaffirm leadership in medical research

It is essential that neonatologists reaffirm their role as neonatal health-care leaders and research coordinators in

Panel 8: **Solutions to barriers encountered by former patients or family representatives and advocacy groups**

Lack of public awareness and trust

- Advocate together with health-care professionals and neonatal professional societies
- Represent the problems of rare neonatal diseases and malformations and connect with other rare disease consortia
- Engage with and involve other former patients, parents, relatives, and caregivers, explaining the importance of patient and public involvement and engagement and its implementation
- Organise public campaigns to raise awareness of the societal value of neonatal health and the burden of neonatal disease
- Support clinicians and scientists in fighting misinformation and fake news and promote public trust in neonatology and medicine

Insufficient funding

- Raise funds through philanthropy and public–private partnerships
- Engage in crowdfunding
- Engage with industry, governments, universities, and academic medical centres

Inadequate research protocols

- Help to prioritise relevant outcomes for research
- Advocate to fully recognise neonatology as a medical specialty and provide research training to younger neonatologists
- Support cross-disciplinary exchange between researchers
- Connect with patient representatives from adult medicine
- Campaign to inform parents about the benefits of participation in medical research

Overcautious ethics committees and regulatory agencies

- Advocate to recognise the need for neonates to participate in high-quality research to improve their care
- Advocate for governance structures that enable neonates to safely benefit from participation in research

medical discussions with research ethics committees, regulatory agencies, and industry. This core involvement will also highlight the role of neonatology within the public health continuum.

Neonatology must be recognised as an academic specialty everywhere, and medical curricula for neonatologists must include dedicated research training. There are striking differences in terms of the number of neonatologists and neonatal nurses between countries, and concerns persist about the capacity of the existing workforce of clinicians and clinician scientists who are trained in neonatal research. The support of practising research clinicians performing translational and clinical studies is crucial.

Moreover, neonatologists caring for the smallest and most fragile patients experience high levels of stress, and burnout is common.[226] Caring for the neonatology workforce demands a high level of attention to the central role of the neonatologist, the quality of their work environment, and securing adequate institutional support.

Leadership challenges in neonatology are part of a broader issue of distrust in medicine and medical research by the general public. Neonatal researchers must proactively address this issue by explaining research data in plain language, fighting online misinformation, advocating for the importance of medical research, and reaffirming the central role of neonatologists for the health care of newborn infants. At the local level, universities, hospitals, and research centres should allocate resources to help physicians with these tasks and enlist the help of external communication experts to provide effective medical leadership training. Training of medical leaders should draw on new technologies and AI. Adequate infrastructure is required to minimise the burden of administrative tasks and foster greater focus on designing and leading high-quality research.

Recommendations for former patients or family representatives and advocacy groups

Representatives and relatives of patients who had severe health issues as newborn infants can be powerful advocates for the concept that clinical research does not compromise outcomes of newborn infants but rather enhances neonatal survival and recovery. Not only can their perspectives add to successful research completion and translation into practice, but their coordinated effort is also likely to positively influence policy and the public perception of research. As such, this stakeholder group has a pivotal role in driving innovation in neonatology. Barriers encountered by former patients or family representatives and advocacy groups are lack of public awareness and trust, insufficient funding, inadequate research protocols, and overcautious ethics committees and regulatory bodies. Solutions to these barriers are presented in panel 8.

Recommendation 1: advocate for more and better neonatal research and development

Former patients and relatives can speak about the societal value of neonatal research and development and medicine, describing the burden of not having an efficacious neonatal drug or devices. The public should hear from former neonatal patients or family representatives as much as possible. Not only are patient and family representatives well placed to increase public awareness, but they can also direct advocacy for neonatal research and development towards other stakeholders, including institutional review boards, ethical boards, regulatory agencies,

funders, universities and academic medical centres, and governmental agencies. Targeting advocacy efforts towards governmental agencies is a particularly powerful way of increasing public funding and changing public perception about neonatal health care and the value of research to society. These activities might also help to create new shared public–private–charity funding opportunities.

There are several ways and occasions to exert this advocacy, and it is up to every organisation to choose the best strategies for the best regional or national impact. When it comes to life-threatening disorders, advocacy is particularly powerful in conjunction with health-care professionals who can provide the scientific background. This is particularly important for rare neonatal disorders.

Recommendation 2: promote awareness and engagement of patients, families, and the public across the clinical research and development pathway

Former patients and family representatives can help to prioritise relevant research questions and study outcomes for high-quality clinical trials. Collaborations with large patient associations from other medical fields might be productive, especially those fields that widely accept the principle that all patients should be offered a clinical trial if no evidence-based standard of care exists for their condition. Families, particularly those that have had negative experiences, can generate questions for researchers and promote greater diversity of research participants.

Recommendation 3: promote public outreach

Cultural, social, and religious backgrounds and past experiences influence public perceptions of risk and acceptability of research and consent processes. People with lived experience, parents, and family members are potent communicators within governments, regulatory bodies, and society. They are particularly helpful in ensuring transparency, trust, and engagement in the research process.

Together with neonatologists and other health-care professionals involved in neonatal medicine, former patients and family representatives can help to fight misinformation and foster trust in science, medicine, and experts. Lay people with direct experience of a disease can shed light on a critical perspective, which is the immediate danger to patients that results from misinformation and a lack of competence, knowledge, expertise, and innovation.

Recommendation 4: improve PPIE support

Former patients and family representatives often encounter practical and financial barriers to PPIE, such as travel, parking, subsistence, and childcare, which can be overcome through reimbursements. PPIE networks can solve logistical problems such as those that occur during holidays and school terms. Alternative methods of communication, such as training videos or podcasts, social networks, virtual meetings, and email, are important to offer, as is the provision of acknowledgments and feedback. While promoting public outreach, former patients and family representatives are powerful allies in explaining the importance of PPIE and its implementation. Former patients and family representatives are often best placed to penetrate social and cultural barriers to PPIE and to deliver campaigns in settings with financial and organisational deficits.

Recommendations for governments, universities, and academic medical centres

Government, universities, and academic medical centres have a crucial role in improving drug and device development and in supporting implementation of innovative technologies and medical advances in neonatology, particularly in countries where health-care systems rely on public funding. Barriers encountered by governments, universities, and academic medical centres are insufficient public awareness and public distrust, insufficient funding, undervalued medical leadership and perception of neonatology as unimportant, and malfunctioning of institutional review boards and

***Panel 9*: Solutions to barriers encountered by governments, universities, and academic medical centres**

Insufficient public awareness and public distrust

- Listen to key opinion leaders in neonatology, researchers, scientific societies, and former patients and family representatives
- Listen to non-governmental and local philanthropic organisations
- Organise public awareness campaigns to educate about the importance of neonatal research
- Promote cultural exchanges between neonatologists, other critical care specialists, and the public

Insufficient funding

- Embrace value-based neonatology principles, considering cost-effectiveness of long-term outcomes for families and society
- Monitor implementation of innovations and assess the quality of care
- Consult key opinion leaders with expertise in neonatology and discuss neonatal research and development with experts, scientific societies, and national ethics committees
- Collaborate with other governments and institutions or engage in private–public partnership to fund shared grants
- Facilitate start-ups that invest in neonatal medicine
- Promote widespread use of health technology assessments in neonatology

Undervalued medical leadership and the perception of neonatology as unimportant

- Create a dedicated academic pathway that offers multidisciplinary training and formally distinguishes between academic roles in neonatology and paediatric specialties
- Create neonatology chairs and professorships
- Work with professional associations and scientific societies to understand what is needed to advance neonatal medicine

regulatory bodies. Solutions to these barriers are summarised in panel 9.

Recommendation 1: embrace value-based neonatology

Politicians and public leaders should be informed about value-based neonatology so that they understand how innovation and research in neonatology is strongly linked to the quality and impact of neonatal health care. To measure the impact of innovation in newborn health, governments, universities, and academic medical centres can incorporate health metrics that capture the lifetime effect of neonatal health care. In this context, effective tools to monitor implementation of innovations and assess care quality are warranted. This issue is partly covered by health technology assessment programmes, which should be strongly promoted in neonatology.

Recommendation 2: commit to a greater investment of resources in neonatal research and development

Politicians and public leaders should allocate a fair amount of funding to neonatal research and development. Financial support for neonatal research and development is crucial and has a high ethical value, particularly in areas in which private industry and academic institutions alone cannot sustain drug and medical device development because of the market size. Funding shortfalls can also be overcome by collaborating with other governments or by engaging in public–private and public–philanthropy partnerships. Start-ups investing in neonatal medicine can also be facilitated. Governments, universities, and academic medical centres should always consider the ethical value of neonatal innovation for families and societies. A good starting point is learning from what has been done for other medical specialties, such as oncology or infectious diseases, for which support from governments, universities, and academic medical centres has been stronger.

Recommendation 3: campaign to increase trust in neonatal medicine

Some governments have used campaigns to explain the importance of and increase trust in medical specialties dealing with life-threatening situations. Such campaigns are urgently needed for neonatology. Governments, universities, and academic medical centres can help to convey the message that individuals benefit from enrolment in a research project and that for life-threatening conditions, the benefits often outweigh the risks.[227,228]

Finally, governments, universities, and academic medical centres can influence the public's perception of neonatal research and medicine, which could translate into a dismantling of the excessive bureaucracy and the often-overcautious stance taken by regulatory agencies and ethical boards. Clear directives to ethical and regulatory bodies are required to overcome some of the obstacles in drug and device research and development and ensure high-quality research.

Recommendation 4: apply more health technology assessments

When health-care systems are publicly funded, governments, universities, and academic medical centres have an important role in the integrated evaluation of multiple new medicines and devices that have been developed for the same purpose. More developed medical specialties and mature health-care systems tend to prioritise the uptake of new medicines and devices effectively, accounting for the available resources. Health technology assessment is the systematic and multidisciplinary evaluation of the properties of health interventions, considering their direct and indirect, short-term and long-term, clinical, and ethical consequences on patients and society. The aim of health technology assessments is to determine the value of medicines and medical devices and to provide guidance on how these should be implemented using an evidence-based, transparent, and accountable process. Health technology assessments have been successfully applied to perinatal and neonatal screening,[229,230] and neonatology would benefit from more widespread use of health technology assessments across the spectrum of diagnostic tests and interventions.[231]

Recommendation 5: recognise neonatology as a medical specialty

The clear recognition of and support for neonatology as a medical specialty and a better-defined pathway to teach and train neonatologists are essential both for care and research. Yet neonatology is not a formal specialty in all countries. Neonatology is considered to be a paediatric subspecialty in some countries and an independent medical specialty in others. It is important that neonatology be officially recognised as the medical specialty that provides health care for patients in the first month of life. A clear multidisciplinary pathway to becoming a neonatologist must be formalised and should include exposure to obstetrics and fetal medicine, anaesthesiology and critical care, paediatric surgery, biomedical engineering, and genetics. Multidisciplinary training is needed to learn how to manage the complex clinical conditions of neonatal patients and to work efficiently in high-technology neonatal unit environments. In some countries, a shortage of paediatric residents might restrict the ability to develop more extensive training focused on neonatology.

Neonatologists in training should have active opportunities to engaged in research, which can further lead to full academic recognition of the specialty. A recent survey by the European Society of Paediatric and Neonatal Intensive Care showed large variations in the

number of neonatology professorships across European countries, with the fewest full professors in countries with the lowest birth rates.[232] Without academic neonatologists involved in research, there will be no innovation, and this medical field will suffer from a chronic stagnation during which neonatal health is unlikely to improve. Obstetricians, fetal medicine specialists, paediatric surgeons, and other specialists involved in neonatal care should support the recognition of neonatology as a formal specialty because it will strengthen their collaboration and ultimately improve patient outcomes.

A global alliance for improved neonatal health

Global leadership is required to coordinate the actions outlined in this Commission and to oversee progress. We therefore propose a mission-oriented Global Alliance for Innovation in Newborn Health (GAINH) to tackle barriers to advancing improved newborn health through high-impact research and innovation.

Industries will remain reluctant to prioritise and accelerate the development of neonatal medicines, diagnostics, and devices without a sizeable and predictable market. This problem can be addressed by pooling requirements and creating a global financing facility that leverages economies of scale, such as in the successful model used by the Global Vaccine Alliance. In the model we envisage, LMICs would initially pay a lower share of the cost of their GAINH-supported products. As a country's income grows, co-financing of payments would gradually increase to cover the full cost. The model requires that public and private sectors

***Panel 10:* Call to action**

Institutional review boards, ethics committees, and regulatory agencies

- Recognise that neonates have a right to better care through the implementation of high-quality basic, translational, and clinical research
- Improve communication among institutional review boards, ethics committees, and regulatory agencies to encourage inclusion of neonates in appropriate research projects, even if these are started in other patient populations
- Develop more appropriate forms of consent specifically designed for neonatal research
- Protect neonates through research by focusing on appropriate outcomes and patients' best interests
- Include neonates in research projects as the default, and exclude them only with a very strong justification
- Recognise neonatologists as crucial medical leaders and advisers for all stages of neonatal research and development
- Create drug development plans specific for neonates

Industry

- Support preclinical and translational research that incorporates important principles of developmental biology and, in general, the highest-quality science; do not engage in research projects not well grounded in terms of pathobiology and pathophysiology
- Establish novel funding models, including collaboration with other funders
- Simplify internal compliance procedures and avoid creating additional barriers and boundaries with deleterious consequences for neonatal research and development
- Accelerate and enhance the research and development pathway

Physicians and allied health-care professionals

- Demand, develop, and support high standards of neonatal training, which include clinical and academic skills needed to perform high-quality preclinical and clinical neonatal research
- Avoid silos to enhance communication among professions and actively collaborate with researchers from diverse medical fields, including relevant adult medicine specialties
- Embrace smarter clinical research and trial design to realise a more personalised neonatology through better identification of disease phenotypes and the application of novel endotyping strategies
- Promote clinical pharmacology studies to understand developmental aspects of specific drug pharmacokinetic and pharmacodynamic properties
- Target meaningful outcomes with well established endpoints
- Reaffirm leadership in medical research
- Actively engage with former patient representatives and advocacy groups during research and development

Former patients or family representatives and advocacy groups

- Advocate for more and better neonatal research and development
- Promote awareness and engagement of patients, families, and the public more broadly in the research and development pathway
- Encourage public outreach to strengthen trust in neonatal medicine

Governments, universities, and academic medical centres

- Embrace value-based neonatology, recognising the impact of perinatal events on late outcomes throughout the lifespan
- Commit to a greater investment of resources in neonatal research and development
- Campaign to increase public trust in neonatal medicine
- Apply more health technology assessments
- Recognise neonatology as a distinct and well defined medical specialty

work together to establish the operational and financing requirements. GAINH governance and oversight could include representation from leading neonatal academic bodies.

Neonatal studies done in HICs have limited generalisability in LMICs and an imbalance exists where the highest research effort is often directed towards the lowest areas of need. For example, in 2019–20, major funders awarded an average US$577 million per year globally for neonatal and stillbirth research but more than 90% of this funding was allocated to organisations in HICs, with most funding for LMICs supporting preclinical or observational studies rather than randomised controlled trials.[233] High costs and fear of litigation in high-risk populations are also frequently cited as major barriers to research. GAINH could help to redress these imbalances through a global network of clinical centres for neonatal research. This global network would be responsible for coordinating research pathways from initial small-scale studies to formal efficacy trials, followed by larger health technology assessments to determine effectiveness and generalisability across diverse populations that will inform health policy and direct resources to deliver at scale. A global neonatal research network that uses real-world data, digital technologies, and innovative study designs and methodologal approaches would have enormous potential to reduce costs and maximise efficiency.

GAINH could address the global skills shortage that adversely affects research and innovation by coordinating clinical research training and defining clinician–scientist career pathways for neonatal physicians, nurses, and allied health professionals. GAINH could provide a platform for stakeholders to shape research agendas and for advocacy to draw the attention of global and local funders, regulators, policy makers, and society to the importance of neonatal studies to improve health across the life course.

GAINH would share this focus on newborn health with established organisations such as the WHO Partnership for Maternal, Newborn and Child Health, Saving Newborn Lives, the Gates Foundation, the European Association for Perinatal Medicine, and the Global Financing Facility for Women, Children and Adolescents. Whereas these organisations primarily target advocacy, training, research funding, education, and financial support for health systems, GAINH would tackle barriers to neonatal research and innovation, thereby complementing these organisations and filling a gap. By working in collaborative partnership, GAINH would amplify the efforts of existing organisations and help to drive recognition of neonatal research and innovation as one of several essential routes to improved infant, child, and population health.

Conclusions and call to action

The *Lancet Child & Adolescent Health* Commission on the future of neonatology was an urgent academic initiative that brought together a wide range of stakeholder representatives who are committed to helping neonatal medicine flourish. Short-term neonatal health and long-term population health can be improved worldwide by addressing the multifactorial issues through medical innovation and leadership, open-minded multidisciplinary and multiprofessional collaboration, commitment from governments, regulatory agencies, and academia, and close involvement and engagement of families and former patients. Our call to action (panel 10) requires collaboration from all stakeholders.

A definitive timeline to achieving these goals is difficult to provide given the various stakeholders involved. However, it will depend especially on the actions of research ethics committees and regulatory agencies, whose overcautious mindsets we seek to change. Public funding for neonatal medicine also depends on the political and economic context, which is influenced by factors beyond our control.

The impact of this Commission should be judged by the increase in high-quality research that translates to new drugs and diagnostics for neonates. All stakeholders can contribute to innovation (figure 5). Not all actions are immediately achievable, but all stakeholders should be held accountable—all stakeholders are needed to overcome the barriers to innovation in neonatology and to realise a better future for neonatal health care. The cost of inaction will be stagnation in neonatal health, which will negatively influence future generations and the whole of society. Inaction is simply morally unacceptable.

Contributors

DDL, SHA, and NM conceived the Commission. DDL, SHA, NM, PD, SK, and WR were members of the Steering Committee, which was responsible for the coordination of the whole project, its methodology, and harmonisation, and were responsible for leading working groups. DDL oversaw, coordinated, and critically reviewed all sections of the report. SHA, DDL, NM, PD, and SK were chairs for the working groups 1,2,3,4, and 5, respectively. SHA, AA-H, SEJ, and MT were members of work group 1 (How can neonatology achieve an efficient research and development pipeline for neonatal medicines?); DDL, MK, JJP, NR, MS-L, and DT were members of work group 2 (How can neonatology achieve an efficient research and development pipeline for neonatal medical devices?); NM, AB, FB, GI, and MH were members of work group 3 (Why is neonatal research and development important for population health and wellbeing?); PD, PDC, JD, AvdH, HF, WT-M, and AZ were members of work group 4 (How can neonatology promote collaboration in neonatal research and development?); SK, J-LO, HZ, VJL-D, and LT were members of work group 5 (How can neonatology strengthen and enhance the recognition of neonatal research and development as a global necessity?). All authors critically reviewed the intellectual content in this report. DDL investigated the skilled work forces in Latin America, South Africa, and France. Members of work group 5 designed the questionnaires for the advisers and collected and interpreted the responses. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AA-H was Chair of Policy and Communications and co-Chair of the Paediatrics and Women's Heath Expert Group at the Faculty of Pharmaceutical Medicine, Royal College of Physicians, London, UK, and co-Chair of the Maternal Health Project Group at the Association of the British Pharmaceutical Industry. SHA received consultancy or lecturer fees from Chiesi Farmaceutici and was a data safety monitoring board (DSMB) member for a clinical trial organised by Bayer Pharmaceuticals in the field of pulmonary hypertension. PDC received funding from the BREATH Consortium for Lung Regeneration, UK Regenerative Medicine Platform Immunology/Medical Research Council, UCL Therapeutic Acceleration Support (TAS), Wellcome and Engineering and Physical Sciences Research Council (EPSRC), and the EU, and has a patent in the field of neonatology. DDL received grants from the Laerdal Foundation, European Society for Paediatric Research (ESPR), and the ESPNIC, paid to the institution; received consulting fees for honoraria for lectures from Medtronic, Masimo, Airway Therapeutics, Vyaire, Chiesi Farmaceutici, AstraZeneca, BI, Natus, BD, and Getinge; is the chair of the DSMB for the phase 1 trial on exosomes to treat bronchopulmonary dysplasia; is a member of the DSMB for a phase 3 trial about surfactant to treat severe bronchiolitis; is the Immediate Past President of ESPNIC (non-profit); has stock options from Ophirex Pharmaceuticals (not vested); received technical research from Getinge and Chiesi Farmaceutici; received fees from Elsevier as an author and from Springer as an editor, and as royalties for books and publications; has one patent in the field of neonatology; and served as WHO temporary adviser on matters of perinatal health. SNDW received paid expert testimony by the Erasmus MC University Medical Center; has a pending patent in the field of neonatology; was a member of the Khondrion Advisory Board, Director of the Board of the (non-profit) Foundation Dutch Knowledge Center Pharmacotherapy for Children (as such responsible for the Dutch Pediatric Formulary), and Director of the Board of the Kinderformulary (full subsidiary of the Foundation Dutch Knowledge Center Pharmacotherapy for Children, and as such responsible for the international collaborations of the Dutch Pediatric Formulary [Austria, Germany, and Norway]), with all payments made to the institution and not to her personally; and board member of the Dutch Society of Clinical Pharmacology and Biopharmaceutics, Vice Chair of the ESPNIC Pharmacology Section, Scientific Chair Dutch Foundation KiddyGoodPills, advisory board member of Dutch Medicines Evaluation Board, and President of the European Society of Developmental Pediatric Perinatal Pharmacology, all unpaid. HF received grants from the US National Institutes of Health (NIH) and was Vice-Chair of the Pediatric Acute Lung Injury and Sepsis Investigators Network. SEJ received NIH and Patient-Centered Outcomes Research Institute grants, Elsevier royalties for editing *Avery's Diseases of the Newborn*, and travel support from the NIH to attend Pediatric Academic Society; and was a DSMB member for the Albino and Tina Ho's K23 trials, Chair of the DSMB on a trial of enteral iron supplementation and intestinal health in preterm infants, and Chair of the COOL PRIME DSMB. MK received lecturer fees from Drager; is the Chair of a DSMB organised by the US National Heart, Lung, and Blood Institute and a member of a DSMB organised by the NIH and by the Canadian MVP; holds a leadership position in the IPOKRaTES Foundation; and is on the Executive Board of the BPD Collaborative. SK received a grant from the Japan Food Institute for a *Bifidobacterium* study; received lecture fees from AstraZeneca, ATOM Medical, Mallinckrodt Pharma, and Sanofi; is a member of JR-031 trial for hypoxic-ischaemic encephalopathy by JCR Pharmaceuticals; received consulting fees from the Japan Council for Quality Health Care and Japan Cranial Medical Examination and Treatment Society; is director of the board of the non-profit organisation of the Neonatal Research Network of Japan; and served as an adviser to the Federation of Asia and Oceania Perinatal Societies, Japanese Organization for NICU Families, and Japan Indonesia Medical Collaboration Association without payment. VJL-D received a Pfizer's Medical Grant (paid to his institution); honoraria as a lecturer and travel support from Chiesi Farmacuetici; and is President of the Comité de Ética en Investigación (IRB) at Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey, in Monterrey, México. J-LO received grants from the Australian and New Zealand Society of Blood Transfusion and the Australian Government Fetal Alcohol Spectrum Disorder Expansion Services (paid to her institution); received honoraria for lecturing and educational activities from the Hunan Children's Hospital fellowship programme, UN Office of Drug Control, and the NSW Ministry of Health; received travel support from several academic societies and non-profit organisations to attend conferences; was a member of the DSMB for the LIFT trial; served as Chair of the Perinatal Substance Use Group, Aust NZ, the Tow Research Committee, South East Sydney Area Health Service, and the UN Office on Drugs and Crime long-term prenatal opioid exposure strategy; received payment for expert testimony from Queensland Coroners Court; and received consulting fees from Mallinkrodt. JJP received grants from the Australian National Health and Medical Research Council, Wellcome Trust, Perron Research Foundation, and CRC-P (Australia); received honoraria from Drager Medical; was a DSMB member for a clinical trial organised by the Hudson Institute; is a member of the Scientific Advisory Committee of and has stock options in VitalTrace. NR has one patent in the field of neonatology. MS-L received research support from AbbVie; consulting fees, lecture honoraria, and meeting support from AstraZeneca; is a member of the DSMB for the first-in-human phase 1 trial on exosomes to treat bronchopulmonary dysplasia by Exobiologics; and was the President of the Union of European Neonatal and Perinatal Societies (non profit). DGT received grants from the National Health and Medical Research Council, the Victorian Government (Australia); received consulting fees or honoraria for lectures from Getinge, Fischer & Paykel, and Chiesi Farmaceutici; is a member of the DSMB for a trial managed by Getinge; and received research materials or assistance from Sentec and SLE. 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FB had travel support for conferences provided by academic societies and non-profit organisations and is Chair of Governance and Ethics Committee for the Partnership for Maternal, Newborn and Child Health, International Advisory Board Chair of the UN University International Institute for Global Health, and Vice President of Fondation Botnar. AB, PD, JD, MH, WR, WT-M, LT, GI, AvdH, AZ, HZ, and NM declare no competing interests.

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