Survival of Infants Born at 22 to 25 Weeks' Gestation Receiving Care in the NICU: 2020–2022

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abstract

OBJECTIVE: To provide contemporary data on infants inborn at 22 to 25 weeks' gestation and receiving care at level 3 and 4 neonatal intensive care units in the United States.

METHODS: Vermont Oxford Network members submitted data on infants born at 22 to 25 weeks' gestation at a hospital with a level 3 or 4 NICU from 2020 to 2022. The primary outcome was survival to hospital discharge. Secondary outcomes included survival without severe complications, length of stay, and technology dependence.

RESULTS: Overall, 22 953 infants at 636 US hospitals were included. Postnatal life support increased from 68.0% at 22 weeks to 99.8% at 25 weeks. The proportion of infants born at 22 weeks receiving postnatal life support increased from 61.6% in 2020 to 73.7% in 2022. For all infants, survival ranged from 24.9% at 22 weeks to 82.0% at 25 weeks. Among infants receiving postnatal life support, survival ranged from 35.4% at 22 weeks to 82.0% at 25 weeks. Survival without severe complications ranged from 6.3% at 22 weeks to 43.2% at 25 weeks. Median length of stay ranged from 160 days at 22 weeks to 110 days at 25 weeks. Among survivors, infants born at 22 weeks had higher rates of technology dependence at discharge home than infants born at later gestational ages.

CONCLUSIONS: Survival ranged from 24.9% at 22 weeks to 82.1% at 25 weeks, with low proportions of infants surviving without complications, prolonged lengths of hospital stay, and frequent technology dependence at all gestational ages.

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WHAT'S KNOWN ON THIS SUBJECT: The management of infants born extremely preterm presents clinicians and families with difficult and complex decisions.

WHAT THIS STUDY ADDS: Contemporary data on interventions and outcomes among infants born extremely preterm helps inform these decisions.

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In recent years, neonatal intensive care has been provided to infants at ever lower gestational ages. From 2014 to 2020 in the United States, the frequency of active treatment among neonates born alive between 22 weeks 0 days and 25 weeks 6 days increased significantly.[1] Although only 2% of infants receiving care in a NICU in the United States are born at 22 to 25 weeks' gestation,[2] these infants present clinicians and families with difficult, often agonizing decisions and place burdens on care management and health care financing.[3]

As the management of infants born at 22 to 25 weeks changes, contemporary data on interventions and outcomes in this population helps inform these decisions. In this study, we present data for infants with gestational ages of 22 to 25 weeks born from 2020 to 2022 in a large and diverse set of hospitals with level 3 and 4 NICUs, which have the full range of technology and capabilities to provide care for all infants born extremely preterm.[4]

METHODS

Vermont Oxford Network (VON) is a voluntary worldwide community of practice dedicated to improving the quality, safety, and value of newborn care through a coordinated program of data-driven quality improvement, education, and research.[5] VON member hospitals contributed standardized data on live births of infants 401 to 1500 grams or 22 0/7 to 29 6/7 weeks' gestational age who were inborn or transferred to the reporting hospital within 28 days of birth.[6] The University of Vermont Institutional Review Board determined that the use of data from the deidentified VON Research Repository for this study was not human subjects research.

Infant Measures

This study included infants inborn from 22 0/7 to 25 6/7 weeks' gestational age without a minimum birth weight at US VON member hospitals with a level 3 or 4 NICU, which was defined as a unit not required by state regulation or local hospital policy to transfer infants for assisted ventilation, from January 1, 2020 to December 31, 2022. We excluded infants with congenital anomalies ($n = 1339$) and birth weights >4 SD greater than the mean by week and sex ($n = 38$).

Definitions for maternal and infant characteristics and interventions at discharge are found in the VON Manual of Operations.[6] Postnatal life support was defined as the receipt of face mask ventilation, nasal continuous positive airway pressure, endotracheal intubation, surfactant therapy, mechanical ventilation, chest compressions, or epinephrine.

Outcomes

The primary outcome was survival to hospital discharge, which applied to all infants, including those who died in the delivery room or were transferred. Infants transferred to another hospital were tracked by the referring hospital for survival status and length of stay until ultimate birth hospitalization discharge.

Secondary outcomes included, among infants receiving postnatal life support, survival, severe complications of prematurity (severe intraventricular hemorrhage, severe bronchopulmonary dysplasia, severe retinopathy of prematurity, periventricular leukomalacia, necrotizing enterocolitis or focal intestinal perforation, or late infection), length of stay, and technology dependence at discharge. Severe intraventricular hemorrhage was defined as grades 3 or 4.[7] Severe bronchopulmonary dysplasia was defined as mechanical ventilation at 36 weeks' postmenstrual age.[8,9] Severe retinopathy of prematurity was defined as stages 3 through 5.[10] Necrotizing enterocolitis was diagnosed using clinical signs and diagnostic imaging findings and included both medical and surgical cases.[6] Late-onset sepsis applied to infants who survived to day 4 from birth and included the recovery of a bacterial pathogen on a specified list from blood or cerebrospinal fluid, coagulase-negative *Staphylococcus* from blood or cerebrospinal fluid, or a fungus obtained from a blood specimen; coagulase-negative *Staphylococcus* also required systemic signs of infection and treatment with intravenous antibiotics for 5 days or more.[6] Survival without severe complications was defined as survival to discharge home without any of the complications defined above. Severe bronchopulmonary dysplasia was imputed as no for infants discharged from the hospital or transferred before the date of week 36 without supplemental oxygen.

Statistical Analysis

Demographics and unadjusted outcomes are presented using standard descriptive statistics. Statistical analyses were performed by using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Overall, 22 953 inborn infants at 636 US hospitals with level 3 and 4 NICUs were included (infants per hospital: median, 26; range, 1 to 228). Birthing people and infant characteristics are described in Table 1. Of people who gave birth at 22 weeks, 13.9% experienced hypertension, 55.9% were exposed to antenatal steroids, 44.3% were exposed to antenatal magnesium sulfate, and 40.7% were exposed to both. Of people who gave birth at 25 weeks, 31.8% experienced hypertension, 91.7% were exposed to antenatal steroids, 81.0% were exposed to antenatal magnesium sulfate, and 79.3% were exposed to both.

The use of postnatal life support was 68.0%, 95.3%, 99.1%, and 99.8% among infants born at 22, 23, 24, and 25 weeks, respectively (Table 1). The proportion of infants

TABLE 1 Birthing Person and Infant Characteristics Among All Infants by Completed Gestational Age Week								
	22 wk (*N* = 2765)		23 wk (*N* = 5349)		24 wk (*N* = 6933)		25 wk (*N* = 7903)	
	n		*n*		*n*		*n*	
Birthing person characteristics								
Hypertension, %	382	13.9%	1056	19.8%	1876	27.2%	2513	31.9%
Chorioamnionitis, %	928	33.9%	1650	31.0%	1759	25.4%	1702	21.6%
Diabetes, %	203	7.4%	368	6.9%	548	7.9%	774	9.8%
Antenatal steroids, %	1540	55.9%	4559	85.5%	6199	89.5%	7240	91.7%
Antenatal magnesium sulfate, %	1219	44.3%	4000	74.9%	5468	79.0%	6398	81.0%
Antenatal steroids and magnesium sulfate, %	1121	40.7%	3866	72.5%	5337	77.1%	6268	79.4%
Vaginal delivery, %	2164	78.3%	2152	40.2%	1884	27.2%	1925	24.4%
Infant characteristics								
Birth wt, g, med (Q1–Q3)	2746	490 (440–540)	5337	570 (510–635)	6927	660 (580–732)	7902	760 (650–850)
Male, %	1450	52.5%	2764	51.7%	3650	52.6%	4104	51.9%
Multiple gestation, %	703	25.4%	1208	22.6%	1398	20.2%	1625	20.6%
Any support, %	1880	68.0%	5100	95.3%	6872	99.1%	7888	99.8%
2020, %	514	61.7%	1620	94.5%	2323	99.3%	2538	99.8%
2021, %	654	68.0%	1749	96.2%	2284	99.0%	2666	99.8%
2022, %	712	73.6%	17.1	95.3%	2265	99.1%	2684	99.9%

Data from inborn infants born from 2020 to 2022 at level 3 and 4 NICUs reported to VON. Information is reported at the infant level and was missing as follows: hypertension, 83 (0.4%); chorioamnionitis, 115 (0.5%); diabetes, 112 (0.5%); antenatal steroids, 40 (0.2%); magnesium sulfate, 42 (0.2%); vaginal delivery, 4 (0.0%); birth weight, 38 (0.2%); sex, 3 (0.0%); multiple gestation, 3 (0.0%); any support, 1 (0.0%). A birthing person may be represented in birthing person characteristics more than once if infants were part of a multiple gestation. *N* represents the total number of infants; *n* represents the number of infants who met the definition for the data item for whom data are available. Data are presented as percentages or median (Q1–Q3) as noted.

born at 22 weeks' gestation receiving postnatal life support increased from 61.6% in 2020 to 73.7% in 2022 and remained stable for infants born at 23, 24, and 25 weeks.

Among all infants, 24.9% born at 22 weeks survived (39.2% died in the delivery room, 8.2% died within 12 hours of admission to the NICU, and 27.7% died after 12 hours of admission), whereas 52.8% born at 23 weeks, 71.1% born at 24 weeks, and 82.1% born at 25 weeks survived (Fig 1).

Among infants who received postnatal life support, survival to discharge from the hospital ranged from 35.4% of infants born at 22 weeks to 82.0% of infants

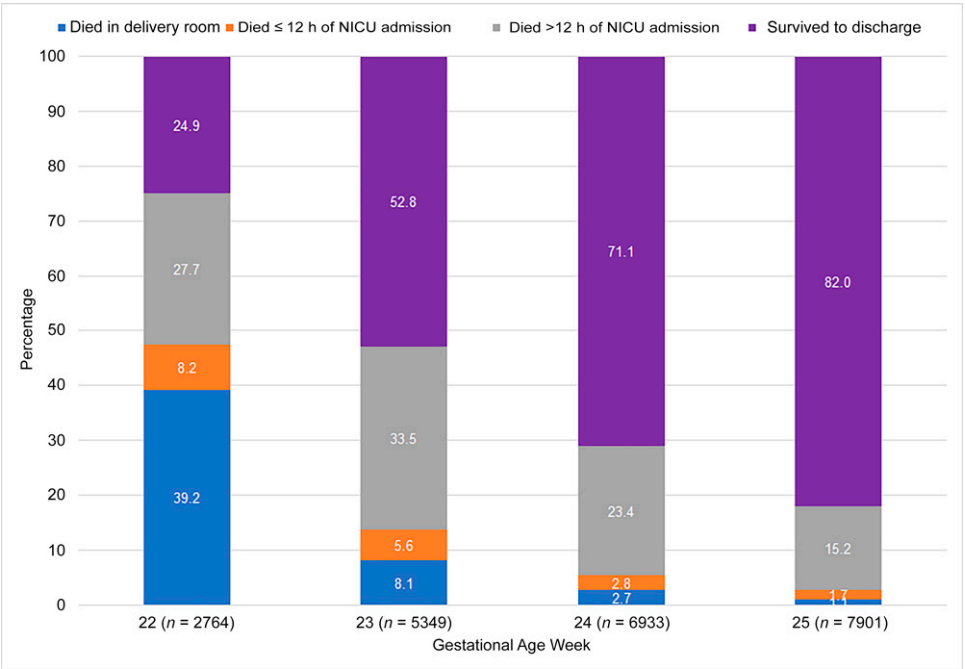

FIGURE 1
Distribution of survival status by gestational age among all infants.

born at 25 weeks and survival without severe complications ranged from 6.3% of infants born at 22 weeks to 43.2% of infants born at 25 weeks (Table 2). Among survivors, infants born at 22 weeks had higher rates of technology dependence at discharge home than infants born at later gestational ages. The median length of stay ranged from 160 days (Q1: 134, Q3: 199) for survivors born at 22 weeks to 110 days (Q1: 94, Q3: 133) for survivors born at 25 weeks.

DISCUSSION

Among 22 953 infants with gestational ages of 22 to 25 weeks born from 2020 to 2022 receiving care at 636 VON US member hospitals, survival ranged from 24.9% at 22 weeks to 82.0% at 25 weeks. The use of postnatal life support increased with gestational age. The proportion of infants born at 22 weeks' gestation receiving postnatal life support increased from 61.6% in 2020 to 73.7% in 2022. Of infants receiving postnatal life support, survival to discharge ranged from 35.4% at 22 weeks to 82.0% at 25 weeks, whereas survival without severe complications ranged from 6.3% at 22 weeks to 43.2% at 25 weeks. These contemporary data should help providers and families who are making decisions about the management of infants born at 22 to 25 weeks' gestation.

Decisions about the obstetric management of extremely preterm births should consider both maternal and infant interests, especially in the face of limited evidence from clinical trials; few of the interventions for infants born extremely preterm have been evaluated in trials, including antenatal corticosteroids.[11] However, with increasing evidence from observational data that antenatal corticosteroid exposure with postnatal life support improved survival compared with no exposure,[12–15] the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommends the consideration of antenatal corticosteroid exposure with counseling starting at 22 0/7 weeks if resuscitation is planned.[16] Magnesium sulfate for neuroprotection has limited evidence from trials and recommendations regarding infants <25 weeks' gestation are unclear.[17] The available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants and that physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.[18] Despite the questions about magnesium sulfate, concomitant exposure to corticosteroids and magnesium sulfate may reduce severe neurodevelopmental impairment or death.[19] In the present study, only 40.7% of those who gave birth to infants at 22 weeks were exposed to both corticosteroids and magnesium sulfate, compared with 72.3%, 77.1%, and 79.3% of those who gave birth to infants at 23, 24, and 25 weeks, respectively. According to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, cesarean delivery for fetal indication is not recommended at 22 weeks' gestation, should be considered at 23 or 24 weeks, and is recommended at 25 weeks.[11] In this study, 78.2% of those who gave birth to infants at 22 weeks had vaginal deliveries, compared with 40.2%, 27.2%, and 24.2% of those who gave birth to infants at 23 weeks, 24 weeks, and 25 weeks, respectively.

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the use of the extremely preterm birth outcomes tool,[20] which estimates outcomes for infants born at 22 to 25 weeks.[11] The estimates were developed from data on infants born at centers participating in the National Institute of Child Health and Development Neonatal Research Network (NICHD NRN) from 2006 and 2012. A study that validated the estimates using data from VON member hospitals for infants born from 2006 to 2016

TABLE 2 Survival, Survival Without Severe Complications, Technology Dependence, and Length of Stay Among Those Receiving Postnatal Life Support by Gestational Age Week

	22 wk (*N* = 1880)		23 wk (*N* = 5100)		24 wk (*N* = 6872)		25 wk (*N* = 7888)	
	n		*n*		*n*		*n*	
Survival	673	36.1%	2794	55.1%	4872	71.5%	6417	82.0%
Survival without complications	112	6.2%	697	14.4%	1686	26.2%	3012	40.9%
Among Survivors	(*N* = 673)		(*N* = 2794)		(*N* = 4870)		(*N* = 6417)	
Tracheostomy	27	4.0%	68	2.4%	104	2.1%	103	1.6%
Gastrostomy tube	89	13.3%	300	10.8%	441	9.1%	396	6.2%
Oxygen	499	74.1%	1905	68.3%	2844	58.4%	2858	44.6%
Monitor	469	69.7%	1802	64.6%	2758	56.7%	2856	44.6%
Length of stay, d, med (Q1–Q3)	670	160 (134–201)	2783	140 (120–170)	4854	127 (109–155)	6400	111 (94–134)

Data from inborn infants born from 2020 to 2022 at level 3 and 4 NICUs reported to VON. Information is reported at the infant level and was missing as follows: survival, 160 (0.7%); survival without morbidity, 1287 (5.9%); tracheostomy, 41 (0.3%); gastrostomy, 41 (0.3%); oxygen, 10 (0.1%); monitor, 15 (0.1%); length of stay, 47 (0.3%). *N* represents the total number of infants; *n* represents the number of infants who met the definition for the data item for whom data are available. Data are presented as percentages or median (Q1–Q3) as noted.

revealed that the hospital of birth contributed equally as much as gestational age.[21] VON offers its members up-to-date hospital-specific estimates of survival on its reporting Web site.[22]

Postnatal life support after birth for infants born at 22 to 25 weeks has increased in recent years.[1,13,23–26] Our study sample includes inborn infants at hospitals with level 3 and 4 NICUs. The most comparable sample, 4635 infants with gestational ages of 22 to 25 weeks born from 2013 to 2018 at 19 academic centers in the NICHD NRN, reported postnatal life support for 36.5% and 88.5% at 22 and 23 weeks' gestation, compared with the rates of 68.0% and 95.3% that we report.[27] Studies using national data from the United States[1,26] and from California[24,25] also have lower rates, but these studies included all infants, regardless of the level of care available at the birth hospital.

Survival of infants born at 22 to 25 weeks' gestation has increased in the United States and other high-income countries.[13,23,26–32] We found that for infants born from 2020 to 2022, survival to hospital discharge among infants receiving postnatal life support was 35.4%, 54.8%, 71.3%, and 81.9% for infants born at 22, 23, 24, and 25 weeks' gestation, respectively. These proportions compare with 10.9%, 49.4%, 69.9%, and 79.2% for infants at those gestational ages born from 2013 to 2018, as reported by the NICHD NRN.[27]

The differences may be explained partially by the more recent cohort that we report. Differences in hospital-level factors may also play a role. Rysavy and colleagues, in a study from the NICHD NRN, found that the initiation of active treatment clustered at the hospital level and differences in practices regarding the initiation of active treatment in extremely preterm infants appear to explain a large portion of the between-hospital variation in survival among such patients.[23] Although the hospital factors responsible for this clustering are not known, attitudes and beliefs about active treatment among neonatal care teams and hospital policies at the 19 academic centers in the NICHD NRN may differ from those at the larger more diverse set of 636 NICUs in the present study, potentially contributing to the higher rates of active resuscitation and survival we observed.

From 2020 to 2022, survival without severe complications during the initial hospitalization ranged from 6.3% at 22 weeks to 43.2% at 25 weeks. The severe complications that we evaluated are all associated with poor developmental outcomes long into childhood.[33–40] Rates of <1% at 22 weeks' gestation to 18% at 25 weeks were reported for infants born extremely preterm in California from 2015 to 2019, although the California study included all births, not just those at hospitals with level 3 and 4 NICUs.[25]

We observed long lengths of hospital stay, ranging from a median of 159 days at 22 weeks' gestation to 110 days at 25 weeks' gestation, with 25% of surviving infants at 22 weeks hospitalized for >193 days and 25% of infants at 25 weeks staying >133 days, resulting in prolonged family separation. Substantial numbers of infants were discharged on oxygen and monitors and with tracheostomies and gastrostomies, creating further stress and financial burdens on families. However, we do not have data after the initial birth hospitalization. In the NICHD NRN, survival with no or minor neurodevelopmental impairment at 22- to 26-month follow-up occurred in 10% of infants born at 22 weeks and nearly 40% at 25 weeks.[27] In a systematic review of same-center cohorts over time, there was no significant change in neurodevelopmental impairment rates in infants born at <27 weeks' gestation or <1000 grams birth weight between 1990 and 2020.[41]

Research on the safety and efficacy of interventions for the obstetric, delivery room, and neonatal management of extremely preterm births is lacking. Few extremely preterm infants, and almost none born at 22 weeks, have been included in randomized trials.[23] However, as postnatal life support at lower gestational ages is increasingly offered to and chosen by families, research to support evidence-based practice is urgently needed, especially because care management designed and developed for infants born at older gestational ages is now used on infants born at earlier gestational ages. Randomized trials for extreme prematurity are challenging to conduct; therefore, well-designed observational studies are also needed. The Multicenter Inventory of Neonatal-Perinatal Interventions of the Tiny Baby Collaborative collects detailed data on outcomes and practices on infants born at 22 to 23 weeks, such as endotracheal tube size.[42] Artificial womb and artificial placenta technologies are innovative approaches with the potential to transform the management of extreme prematurity.[43,44] Randomized trials of these technologies are on the horizon raising important ethical questions about the management of extreme prematurity.[45,46]

Targeted quality improvement has the potential to improve outcomes for extremely preterm infants and their families. Perhaps most important is improving communication and shared decision-making with families about the obstetric, delivery room, and neonatal management of extremely preterm deliveries, as outlined over 30 years ago.[47,48] The American Academy of Pediatrics guidelines state that decisions regarding life support for infants born extremely preterm should be shared with the family, guided by considering both the likelihood of death or morbidity and the parents' desires for their unborn child.[46] Improvement efforts that address how risks are communicated and how these difficult decisions are made and implemented are of critical importance. Other potential areas for improvement include discharge readiness,[49] establishing dedicated small baby units and teams,[50–52] and adopting the model of family integrated care and early continuous skin-to-skin care.[53–55]

The ultimate goal of neonatal intensive care is to achieve the long-term health and well-being of infants and their families, in which health is understood in the broadest of terms, not just from a biomedical perspective.[56] Adverse clinical events experienced in the neonatal period are only one factor in long-term well-being; the social determinants of health play a significant and perhaps predominant role.[57,58] To achieve better outcomes for infants and families, we must accept our responsibility to follow through, practicing social as well as technical medicine, improving the health and well-being of infants and families by addressing the social determinants of health and promoting equity.[59,60] This need is important, particularly given the well-documented but poorly understood differences in the provision of postnatal life support for infants born extremely preterm.[1,61–63] Additionally, financial burdens and parental stress associated with prolonged lengths of stay and technology dependence at discharge will fall most heavily on families who are economically disadvantaged and socially stressed. Follow-through may provide the greatest opportunity in the near term for improvement for the infants and families we serve.

Mortality rates are higher among preterm infants born in hospitals with a low-level or mid-level NICU than among those born in hospitals with a high-level NICU.[64–66] However, the proportion of extremely preterm births occurring at hospitals with lower-level NICUs increased between 2009 and 2020.[67] Reversing this trend toward de-regionalization will require state policies enforcing certification criteria for the care of extreme prematurity.[68] By establishing and implementing risk-appropriate neonatal care standards, the NICU Verification Program of the American Academy of Pediatrics can improve outcomes for extreme prematurity by ensuring that every infant receives care in a facility with the personnel and resources appropriate for the newborn's needs and condition.[69] This need is of particular importance for extremely preterm births.

Our study includes standardized reporting in recent years by a large and diverse set of hospitals. However, we restricted our analysis to infants born at hospitals with level 3 and 4 NICUs to reflect infants born at facilities best able to care for infants born extremely preterm. Therefore, our data should not be interpreted as providing results for all births at 22 to 25 weeks because many occur at hospitals without level 3 or 4 NICUs. In addition, our study does not include infants transferred to hospitals that do not have delivery services because care for infants born extremely preterm begins in the delivery room; however, many infants born at 22 to 25 weeks may be transferred to such facilities shortly after birth. Finally, the period for this study includes the severe acute respiratory syndrome coronavirus 2 pandemic. The increased use of personal protective equipment and changes in hospital policies could have influenced outcomes.

CONCLUSIONS

Of infants inborn at level 3 and 4 NICUs receiving postnatal life support, overall survival ranged from 24.9% at 22 weeks to 82.0% at 25 weeks. Among infants receiving postnatal life support, survival to discharge ranged from 35.4% at 22 weeks to 81.8% at 25 weeks, whereas survival without severe complications ranged from 6.3% at 22 weeks to 43.2% at 25 weeks, with long lengths of stay and technology dependence at discharge. Research to identify new interventions for the obstetric, delivery room, and neonatal management of extreme preterm birth, quality improvement to reliably apply current evidenced based practices, follow-through to address social determinants of health, and policies to ensure that extreme preterm births are cared for at hospitals with the appropriate facilities, services, and staff may help improve outcomes.

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ABBREVIATIONS

NICHD NRN: National Institute for Child Health and Development Neonatal Research Network
VON: Vermont Oxford Network

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