Research Paper

A global point prevalence survey of antimicrobial use in neonatal intensive care units: The no-more-antibiotics and resistance (NO-MAS-R) study

Pavel Prusakov, PharmD[a], Debra A. Goff, PharmD[b], Phillip S. Wozniak, BA[c],
Azraa Cassim, BPharm[d], Catherine E.A. Scipion, MD[e], Soledad Urzúa, MD[f], Andrea Ronchi, MD[g],
Lingkong Zeng, MD[h], Oluwaseun Ladipo-Ajayi, MBChB[i], Noelia Aviles-Otero, MD[j],
Chisom R. Udeigwe-Okeke, MBBS[k], Rimma Melamed, MD[l], Rita C. Silveira, MD[m],
Cinzia Auriti, MD[n], Claudia Beltrán-Arroyave, MD[o], Elena Zamora-Flores, MD[p],
Maria Sanchez-Codez, MD[q], Eric S. Donkor, PhD[r], Satu Kekomäki, MD[s], Nicoletta Mainini, MD[t],
Rosalba Vivas Trochez, MD[u], Jamalyn Casey, PharmD[v], Juan M. Graus, MD[w],
Mallory Muller, PharmD[x], Sara Singh, MBBS[y], Yvette Loeffen, MD[z],
María Eulalia Tamayo Pérez, MD[aa], Gloria Isabel Ferreyra, MD[ab], Victoria Lima-Rogel, MD[ac],
Barbara Perrone, MD[ad], Giannina Izquierdo, MD[ae], María Cernada, MD[af],
Sylvia Stoffella, PharmD[ag], Sebastian Okwuchukwu Ekenze, MD[ah],
Concepción de Alba-Romero, MD[ai], Chryssoula Tzialla, MD[aj], Jennifer T. Pham, PharmD[ak],
Kenichiro Hosoi, MD[al], Magdalena Cecilia Calero Consuegra, MD[am], Pasqua Betta, MD[an],
O. Alvaro Hoyos, MD[ao], Emmanuel Roilides, MD[ap], Gabriela Naranjo-Zuñiga, MD[aq],
Makoto Oshiro, MD[ar], Victor Garay, MD[as], Vito Mondì, MD[at], Danila Mazzeo, MD[au],
James A. Stahl, PharmD[av], Joseph B. Cantey, MD[aw], Juan Gonzalo Mesa Monsalve, MD[ax],
Erik Normann, MD[ay], Lindsay C. Landgrave, PharmD[az], Ali Mazouri, MD[ba],
Claudia Alarcón Avila, MD[bb], Fiammetta Piersigilli, MD[bc], Monica Trujillo, MD[bd],
Sonya Kolman, BPharm[be], Verónica Delgado, MD[bf], Veronica Guzman, MD[bg],
Mohamed Abdellatif, FRCPCH[bh], Luis Monterrosa, MD[bi], Lucia Gabriella Tina, MD[bj],
Khalid Yunis, MD[bk], Marco Antonio Belzu Rodriguez, MD[bl], Nicole Le Saux, MD[bm],
Valentina Leonardi, MD[bn], Alessandro Porta, MD[bo], Giuseppe Latorre, MD[bp],

* Corresponding author at: Divisions of Neonatology and Pediatric Infectious Diseases, Nationwide Children's Hospital - The Ohio State University College of Medicine, Center for Perinatal Research, Abigail Wexner Research Institute at Nationwide Children's Hospital, 700 Children's Drive, RB3, WB5245, Columbus, Ohio 43205-2664, United States.
E-mail addresses: pavel.prusakov@nationwidechildrens.org (P. Prusakov), Debbie.Goff@osumc.edu (D.A. Goff), phillip.wozniak@osumc.edu (P.S. Wozniak), ladyaz786@gmail.com (A. Cassim), cscipion@haitihealth.org (C.E.A. Scipion), soleurzua@gmail.com (S. Urzúa), a.ronchi83@gmail.com (A. Ronchi), freeman315@163.com (L. Zeng), yawy2@yahoo.com (O. Ladipo-Ajayi), naviote7f@gmail.com (N. Aviles-Otero), adaobisom@yahoo.com (C.R. Udeigwe-Okeke), rimmam@bgu.ac.il (R. Melamed), drarita.c.s@gmail.com (R.C. Silveira), cinzia.auriti@opbg.net (C. Auriti), claumd77@hotmail.com (C. Beltrán-Arroyave), zamoraflores@hotmail.com (E. Zamora-Flores), mscodez1990@gmail.com (M. Sanchez-Codez), ericsdon@hotmail.com (E.S. Donkor), satu.kekomaki@hus.fi (S. Kekomäki), nicmainini@yahoo.it (N. Mainini), rossyviv@hotmail.com (R.V. Trochez), Jamalyn.Casey@ascension.org (J. Casey), juan.m.graus@gmail.com (J.M. Graus), Mallory.Muller@orlandohealth.com (M. Muller), sara.divah@gmail.com (S. Singh), Y.G.T.Loeffen-2@umcutrecht.nl (Y. Loeffen), eulalia.tamayo@udea.edu.co (M.E.T. Pérez), glorietaferrey@yahoo.com.ar (G.I. Ferreyra), limamv@hotmail.com (V. Lima-Rogel), barbara.perrone7@gmail.com (B. Perrone), gianninai@yahoo.es (G. Izquierdo), mariacernada@gmail.com (M. Cernada), Sylvia.Stoffella@ucsf.edu (S. Stoffella), sebekenze@gmail.com, sebastian.ekenze@unn.edu.ng (S.O. Ekenze), concha.dealbaromero@gmail.com (C. de Alba-Romero), c.tzialla@smatteo.pv.it (C. Tzialla), Tran@uic.edu (J.T. Pham), hosoi-k@ks.kyorin-u.ac.jp (K. Hosoi), magdacalero@yahoo.com (M.C.C. Consuegra), mlbetta@yahoo.it (P. Betta), alvaromicro@hotmail.com (O.A. Hoyos), roilides@gmail.com (E. Roilides), gabinarzu@gmail.com (G. Naranjo-Zuñiga), makoto@nagoya-1st.jrc.or.jp (M. Oshiro), garayvic@gmail.com (V. Garay), vito.mondi@mail.it (V. Mondì), danilamazzeo@outlook.it (D. Mazzeo), James.Stahl@nortonhealthcare.org (J.A. Stahl), cantey@uthscsa.edu (J.B. Cantey), jgmesa1981@yahoo.com (J.G.M. Monsalve), erik.normann@akademiska.se (E. Normann), Lindsay.c.landgrave@gsk.com (L.C. Landgrave), mazouriali@yahoo.com (A. Mazouri), claudiaalarconavila@gmail.com (C.A. Avila), Fiammetta.piersigilli@uclouvain.be (F. Piersigilli), trupitv@gmail.com (M. Trujillo), Sonya.Kolman@nmch.org.za (S. Kolman), veritamd@icloud.com (V. Delgado), draverolui@gmail.com (V. Guzman), mabdelmonem2015@gmail.com (M. Abdellatif), Luis.Monterrosa@HorizonNB.ca (L. Monterrosa), gabriella.tina@tiscali.it (L.G. Tina), kayunis@aub.edu.lb (K. Yunis), drmarcobr@gmail.com (M.A.B. Rodriguez), Lesaux@cheo.on.ca (N.L. Saux), valentinaleo83@yahoo.it (V. Leonardi), alessandro-porta@tiscali.it (A. Porta), g.latorre@miulli.it (G. Latorre), n0n.hide@med.kitasato-u.ac.jp (H. Nakanishi), MI_MEIR@rambam.health.gov.il (M. Meir), paolomanzoni@hotmail.com (P. Manzoni), xnorero@gmail.com (X. Norero), ahoyos@clinicadelcountry.com (A. Hoyos), dianaarias@hotmail.com (D. Arias), rubennigue@hotmail.com (R.G. Sánchez), Alexandra.Medoro@nationwidechildrens.org (A.K. Medoro), Pablo.Sanchez@nationwidechildrens.org (P.J. Sánchez).

Hidehiko Nakanishi, MD[bq], Michal Meir, MD[br], Paolo Manzoni, MD[bs], Ximena Norero, MD[bt], Angela Hoyos, MD[bu], Diana Arias, MD[bv], Rubén García Sánchez, MD[bw], Alexandra K. Medoro, MD[c,bx], Pablo J. Sánchez[c,bx,*], for the Global NEO-ASP Study Group

[a] *Department of Pharmacy, Nationwide Children's Hospital, Columbus, OH, USA*
[b] *Department of Pharmacy, The Ohio State University Wexner Medical Center, The Ohio State University College of Pharmacy, Columbus, OH, USA*
[c] *The Ohio State University College of Medicine, Columbus, OH, USA*
[d] *Chris Hani Baragwanath Hospital, Johannesburg, South Africa*
[e] *Health Equity International, Fond- des- Blancs, Haiti*
[f] *Department of Neonatology, Pontificia Universidad Catolica, Santiago, Chile*
[g] *Division of Neonatology and NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[h] *Department of Neonatology, Wuhan Children's Hospital Wuhan Maternal and Child Healthcare Hospital Tongji Medical College Huazhong University of Science & Technology, Wuhan, China*
[i] *Department of Pediatric Surgery, Lagos University Teaching Hospital, Lagos, Nigeria*
[j] *University of Virginia School of Medicine, Charlottesville, VA, USA*
[k] *Division of Paediatric Surgery, National Hospital, Abuja, Nigeria*
[l] *Pediatric Infectious Diseases Unit and Faculty of Health Sciences, Ben Gurion University of the Negev, Soroka University Medical Center, Beer Sheva, Israel*
[m] *Department of Pediatrics, Newborn Section, Universidade Federal do Rio Grande do Sul. Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil*
[n] *Department of Neonatology, Bambino Gesù Children's Hospital, Rome, Italy*
[o] *Clinica del Prado and Clinica El Rosario, Medellin, Colombia*
[p] *Division of Neonatology, Hospital Materno Infantil Gregorio Marañon University Hospital, Madrid, Spain*
[q] *Division of Pediatric Infectious Diseases, Puerta del Mar University Hospital, Cadiz, Spain*
[r] *Department of Medical Microbiology, University of Ghana Medical School, Accra, Ghana*
[s] *Division of Pediatric Infectious Diseases, Children's Hospital, Helsinki University Hospital, Helsinki, Finland*
[t] *Division of Neonatology, Treviso Hospital, Treviso, Italy*
[u] *Clinica Soma, Procaren NICU, CES University, Medellin, Colombia*
[v] *Department of Pharmacy, St. Vincent Women's Hospital, Indianapolis, IN, United States*
[w] *Department of Neonatology, Hospital Nacional Cayetano Heredia, Lima, Peru*
[x] *Department of Pharmacy, Arnold Palmer Hospital for Children, Orlando, FL, USA*
[y] *University of Guyana, School of Medicine, Georgetown, Guyana*
[z] *Division of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, Utrecht, Netherlands*
[aa] *Coordinator of Neonatology Fellow Program, Head of Neonatal Intensive Care, University of Antioquia, Hospital San Vicente Fundacion, Medellin, Colombia*
[ab] *Department of Neonatology, Instituto de Maternidad Ntra. Sra. de las Mercedes, San Miguel de Tucumán, Argentina*
[ac] *Division of Neonatology, Hospital General Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico*
[ad] *Division of Neonatology and NICU, G. Salesi Children's Hospital, Ancona, Italy*
[ae] *Division of Neonatology and Pediatric Infectious Diseases, Hospital Barros Luco Trudeau, Santiago, Chile*
[af] *Division of Neonatology and Neonatal Research Group, La Fe University and Polytechnic Hospital, Valencia, Spain*
[ag] *Department of Pharmacy, UCSF Benioff Children's Hospital, San Francisco, CA, USA*
[ah] *Sub-Department of Pediatric Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria*
[ai] *Division of Neonatology, Hospital 12 de Octubre, Madrid, Spain*
[aj] *Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[ak] *Department of Pharmacy, University of Illinois Hospital & Health Sciences System, Chicago, IL, USA*
[al] *Department of Pediatrics, Kyorin University School of Medicine, Tokyo, Japan*
[am] *Division of Neonatology, Hospital General San Francisco, Quito, Ecuador*
[an] *Division of Neonatology and NICU, AOU Policlinico G Rodolico, Catania, Italy*
[ao] *Clínica Universitaria Bolivariana/Universidad Pontificia Bolivariana, Medellín, Colombia*
[ap] *Infectious Diseases Unit, 3rd Department of Pediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Thessaloniki, Greece*
[aq] *Division of Pediatric Infectious Diseases, Hospital Nacional de Niños, San Jose, Costa Rica*
[ar] *Department of Pediatrics, Nagoya Red Cross Daiichi Hospital, Nagoya, Japan*
[as] *Division of Neonatology, Alberto Sabogal Hospital, Lima, Peru*
[at] *Policlinico Casilino, Rome, Italy*
[au] *Division of Patology and Intensive Neonatal Care, A.O.U. Policlinico di Messina, Messina, Italy*
[av] *Department of Pharmacy, Norton Children's Hospital, Louisville, KY, USA*
[aw] *Department of Pediatrics, Division of Neonatology, University Hospital UT Health San Antonio, San Antonio, TX*
[ax] *Pediatric Infectious Diseases, Hospital General de Medellín, Medellín, Colombia*
[ay] *Department of Women's and Children's Health, Uppsala University, Uppsala University Children's Hospital, Uppsala, Sweden*
[az] *Department of Pharmacy, Parkview Regional Medical Center, Fort Wayne, IN, USA*
[ba] *Iran University of Medical Sciences, Tehran, Iran*
[bb] *Department of Perinatology and Neonatology, Central Military Hospital, Nueva Granada Military University, Bogotá, Colombia*
[bc] *Department of Neonatology, Cliniques Universitaires Saint Luc, Brussels, Belgium*
[bd] *Program Coordinator Pediatric Infectious Diseases Clinica Universiraria Bolivariana, Hospital Pablo Tobon Uribe, Medellin, Colombia*
[be] *Department of Pharmacy, Nelson Mandela Children Hospital, Johannesburg, South Africa*
[bf] *Head of Neonatal Intensive Care, Hospital de los Valles, Quito, Ecuador*
[bg] *Pontificia Universidad Catolica del Ecuador, Hospital Metropolitano Quito, Quito, Ecuador*
[bh] *Child Health Department, Sultan Qaboos University Hospital, Muscat, Oman*
[bi] *Department of Pediatrics, Division of Neonatology, Saint John Regional Hospital, Saint John, Canada*
[bj] *Head of NICU Department, ARNAS Garibaldi, Catania, Italy*
[bk] *Division of Neonatology, American University of Beirut Medical Center, Beirut, Lebanon*
[bl] *Division of Neonatology, Maternal and Children Hospital of Tigre Dr. Florencio Escardó, Tigre, Argentina*
[bm] *Division of Infectious Disease, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada*
[bn] *Division of Neonatology and NICU, Careggi Univerisity Hospital, Florence, Italy*
[bo] *G. Fornaroli Hospital, Magenta, Milan, Italy*
[bp] *Ospedale Miulli, Acquaviva, Italy*
[bq] *Research and Development Center for New Medical Frontiers, Department of Advanced Medicine, Division of Neonatal Intensive Care Medicine, Kitasato University School of Medicine, Sagamihara, Japan*
[br] *Division of Pediatric Infectious Diseases, The Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel*
[bs] *Division of Pediatrics and Neonatology, Degli Infermi Hospital, Biella, Italy*
[bt] *Hospital del Niño, Panama, Panama*
[bu] *Division of Neonatology, Clínica del Country / Clínica La Colina, Bogotá, Colombia*

bv *Hospital San Jose, Bogotá, Colombia*
bw *Hospital Universitario de Salamanca, Salamanca, Spain*
bx *Department of Pediatrics, Divisions of Neonatology and Pediatric Infectious Diseases, Nationwide Children's Hospital, Center for Perinatal Research, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA*

ARTICLE INFO

ABSTRACT

Background: Global assessment of antimicrobial agents prescribed to infants in the neonatal intensive care unit (NICU) may inform antimicrobial stewardship efforts.

Methods: We conducted a one-day global point prevalence study of all antimicrobials provided to NICU infants. Demographic, clinical, and microbiologic data were obtained including NICU level, census, birth weight, gestational/chronologic age, diagnoses, antimicrobial therapy (reason for use; length of therapy), antimicrobial stewardship program (ASP), and 30-day in-hospital mortality.

Findings: On July 1, 2019, 26% of infants (580/2,265; range, 0−100%; median gestational age, 33 weeks; median birth weight, 1800 g) in 84 NICUs (51, high-income; 33, low-to-middle income) from 29 countries (14, high-income; 15, low-to-middle income) in five continents received ≥1 antimicrobial agent (92%, antibacterial; 19%, antifungal; 4%, antiviral). The most common reasons for antibiotic therapy were "rule-out" sepsis (32%) and "culture-negative" sepsis (16%) with ampicillin (40%), gentamicin (35%), amikacin (19%), vancomycin (15%), and meropenem (9%) used most frequently. For definitive treatment of presumed/confirmed infection, vancomycin (26%), amikacin (20%), and meropenem (16%) were the most prescribed agents. Length of therapy for culture-positive and "culture-negative" infections was 12 days (median; IQR, 8−14) and 7 days (median; IQR, 5−10), respectively. Mortality was 6% (42%, infection-related). An NICU ASP was associated with lower rate of antibiotic utilization ($p = 0.02$).

Interpretation: Global NICU antibiotic use was frequent and prolonged regardless of culture results. NICU-specific ASPs were associated with lower antibiotic utilization rates, suggesting the need for their implementation worldwide.

Funding: Merck & Co.; The Ohio State University College of Medicine Barnes Medical Student Research Scholarship

Research in context

Evidence before this study

Excessive antibiotic use among preterm infants in the neonatal intensive care unit (NICU) has been associated with adverse patient outcomes as well as unit-level and public health consequences such as emergence of multi-drug resistant organisms and higher health-care costs. Antibiotic therapy in NICUs varies widely among institutions irrespective of level of NICU care, medical morbidities, and proven bloodstream infection. Previous global point prevalence studies have included both pediatric and neonatal populations, with little focus on the quantity and reasons for their use. We searched PubMed with the following terms: point prevalence, antimicrobial agent, antibiotic, neonate, NICU with no language restrictions although only English publications subsequently were reviewed. We reviewed publications on NICU antimicrobial stewardship before September 2020.

Added value of this study

We found that 26% of infants in 84 NICUs from 29 countries (14, high-income and 15, low-to-middle income) received at least one antimicrobial agent on July 1, 2019. Antibiotics (92%) were most frequently used while 19% and 4% of infants received antifungal and antiviral agents, respectively. The antimicrobial utilization per NICU in low-to-middle income countries was significantly greater than in NICUs of high-income countries, while centers that had an NICU-specific Antimicrobial Stewardship Program had lower antibiotic utilization rates regardless of the country's income level.

Implications of all the available evidence

The finding that NICU-specific antimicrobial stewardship programs had a positive impact on antibiotic utilization highlights the potential value of such programs to reduce antibiotic consumption and possibly minimize the adverse effects of antimicrobial overuse in high-risk infants. In addition, global assessment of all antimicrobial use provided to infants in the NICU and reasons for their use should inform future antimicrobial stewardship efforts.

1. Introduction

Antimicrobial agents are the most prescribed medications in the neonatal intensive care unit (NICU) [1,2]. When used for proven infections, antibiotics have dramatically improved survival in this high-risk population [3,4]. However, by presumed disruption of the infant's bacterial microbiome, antibiotic overuse has been associated with adverse patient outcomes such as late-onset sepsis, invasive candidiasis, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, neurodevelopmental impairment, and even death [5−13]. In addition, antibiotic overuse can result in unit-level and public health consequences such as emergence of multi-drug resistant organisms and higher health-care costs [14,15]. Despite this knowledge and associations, the use of antibiotic therapy in NICUs varies widely among institutions in the United States irrespective of level of NICU care, medical morbidities, and proven bloodstream infection [16−18]. Although it is likely that similar variation exists among NICUs worldwide [19−24], there has been little focus on why and how antibiotics are used on a global scale.

Accordingly, the objectives of the NO-More-AntibioticS and Resistance (NO-MAS-R) study was to 1) determine a single day global prevalence of all antimicrobial use and specific agents provided to infants in the NICU; 2) quantify the clinical diagnoses why infants received antimicrobial therapy; and 3) quantify the proportion of antibiotics that were started empirically, targeted to an identified pathogen, or used for prophylaxis. We hypothesized that a substantial proportion of infants in NICUs worldwide would be exposed to antimicrobial therapy. Our ultimate goal was that global assessment of all antimicrobial use provided to infants in the NICU and reasons for their use will inform future antimicrobial stewardship efforts.

2. Methods

2.1. Design and setting

This cross-sectional, observational study enrolled all infants who were in the NICU and prescribed at least one antimicrobial agent as of 8 AM or later (local time) on July 1, 2019, the birthday of Ignaz Semmelweiss, MD, the "Father of Hand Hygiene" and "Savior of Mothers and Newborns [25]." Pediatricians, neonatologists, pediatric infectious diseases specialists, and pediatric pharmacists from around the world were queried to determine their interest in participating in a survey of antibiotic practices in infants admitted to Level II, III, or IV NICUs. These classifications of neonatal inpatient care consist of increasing level of specialty care (Level II) and subspecialty intensive care (Levels III and IV) [26]. Infants in Level II NICUs are born at ≥32 weeks' gestation weighing ≥1500 g with medical problems that are expected to resolve rapidly. Level III NICUs are able to provide sustained life support for the most complex and critically ill infants <32 weeks' gestation, weighing <1500 g at birth, or have medical or surgical conditions regardless of gestational age. Level IV NICUs have the capabilities of a Level III NICU plus provide on-site surgical repair of serious congenital or acquired malformations.

2.2. Participants and study procedures

The following data were collected on each infant: pertinent demographic and clinical information including birth weight, gestational and chronologic age, diagnoses, name of antimicrobial agent(s) prescribed and received, routes of administration, reason for its use, planned length of therapy, and culture results. In addition, information was obtained on the geographic location of the NICU, NICU level, NICU census, referral or delivery NICU, and existence of an antimicrobial stewardship program (ASP) either in the hospital or specific to the NICU. An NICU-specific ASP consisted of dedicated personnel in the NICU who supervise antibiotic use and/or had specific guidelines on antimicrobial use for the NICU. Finally, a 30-day follow-up assessment was performed to determine actual length of antimicrobial therapy for each agent prescribed as well as infant outcomes (discharged home, transferred to another facility, or in-hospital death). In addition, the infection-related in-hospital mortality was assessed at 30 days by review of the attending physician's documentation in the medical record and/or autopsy report if available. The 30-day mortality has been the standard used by the Centers for Medicare & Medicaid Services of the United States to assess quality of medical and surgical care and has been used in pediatric patients for assessment of sepsis mortality [27,28]. Antibiotic use was compared among infants who were less than three days of age versus those three days of age or older in keeping with evaluations for early vs. late-onset infections and sepsis, respectively.

Diagnostic terms were defined to assure consistency among sites. An antimicrobial agent was defined as a drug that exhibits activity against a bacterial, fungal, or viral pathogen. Prophylactic therapy was defined as an antimicrobial agent prescribed to prevent an infection. Empiric therapy was defined as initiation of an antimicrobial

agent for suspected infection with the intent of discontinuing such therapy once infection was ruled out. Definitive therapy was defined as antimicrobial therapy that was continued to cure an infection that was substantiated by clinical and/or microbiologic diagnostics. "Rule-out sepsis" was defined as initiation of antimicrobial therapy for infants who were undergoing evaluation for a possible bloodstream infection with intent to discontinue therapy if the culture(s) were sterile at 24 to 72 h. "Culture-negative" sepsis or meningitis was defined as a clinical diagnosis of a bloodstream or central nervous system infection, respectively, with sterile bacterial cultures and no viral or fungal pathogen identified.

Antibiotics were grouped by the Access, Watch, Reserve ("AWaRe") classification on the basis of the World Health Organization's (WHO) Essential Medicines List for Children and their use compared among NICUs in Asia, Europe, Africa, North America, Central America, and South America [21,29,30]. The Access group contains more narrow-spectrum antibiotics, the Watch group contains broader spectrum antibiotic classes, and the Reserve group consists of antibiotics reserved for multidrug resistant infections.

2.3. Data sources

The study survey and data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based software platform hosted at Nationwide Children's Hospital [31,32]. A study investigator at each site entered de-identified data either real time or retrospectively if real time entry was not feasible. In case of technical difficulties with REDCap, local site investigators entered de-identified data using an Excel spreadsheet that was subsequently entered into REDCap by the study coordinator at Nationwide Children's Hospital. The data collection tool was piloted on December 12, 2018 with 12 international sites to identify any data collection challenges. Modifications were made based on participants' feedback.

Although we were not able to perform external data validation at each site, procedures were implemented to minimize data entry errors. Each participating site was provided a Manual of Operations with standard definitions, the REDCap data entry had restriction on numbers entered, all names of antimicrobial agents were selected from a drop-down menu, and the Excel database had prefilled parameters to facilitate data acquisition. In addition, we queried sites if there was concern for entered data.

2.4. Ethics statement

The study was approved by the Institutional Review Board (IRB) at Nationwide Children's Hospital under the following designated number: STUDY00000208. Invitation letter, study protocol in English or Spanish, and the Nationwide Children's Hospital IRB approval letter were provided to each participating site for submission to the local IRB. Each site was responsible for obtaining ethics approval if required by their institution. Since all data were anonymized without patient identifiers and there was no direct contact with patients, the study at all sites was exempt from the need to obtain informed consent.

2.5. Statistical analysis

Descriptive statistics and graphical presentation of the data were done by means of Microsoft Excel. Comparative statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26·0. Armonk, NY: IBM Corp. For categorical data, chi-squared or Fisher exact tests were used for comparison as well as analysis of dependence. For normally distributed continuous data, means with standard deviation were derived for descriptive statistics and analyzed with two-sample t-test [33]. All nonparametric data were reported as median with interquartile range (IQR) and analyzed with

independent-samples Mann-Whitney U test. For accuracy, missing data were not imputed.

2.6. Role of the funding source

The funding agency had no influence on study design, data collection, or analysis. The corresponding author had full access to the data and is responsible for the decision to submit for publication.

3. Results

3.1. Demographics

On July 1, 2019, 580 (26%) of 2265 infants in 84 hospital NICUs in 29 countries (14 high and 15 low-to-middle income countries, Fig. 1) received at least one antimicrobial agent. Of the 84 NICUs, 51 (61%) and 33 (39%) were in high and low-to-middle income countries, respectively, with a median of 5 infants per site in both high (IQR, 2−9) and low-to-middle (IQR, 3−9) income countries. Sixty-two (74%) NICUs were in hospitals that had a labor and delivery service and the rest in referral centers that cared for outborn infants. All but 4 NICUs were Level 3 (n = 42, 50%) or Level 4 (n = 38; 46%). The antimicrobial utilization per NICU in low-to-middle income countries (31%, median; IQR, 17%−48%) was significantly greater than in NICUs of high-income countries (18%, median; IQR, 10%−36%; p = 0·0013).

Of the 580 infants who received an antimicrobial agent, 83% were ≥3 days of age, the median gestational age was 33 weeks (IQR, 28−37 weeks), median birth weight was 1800 g (IQR, 1060−2840 g), and median postnatal age was 11 days (IQR, 4−33 days) (Table 1). Most of the infants were male (59%) and 23% (n = 133) were <28 weeks' gestation (Table 1). Their characteristics and outcome by global region are provided in Supplementary Table 1. Antibacterials were the most frequently used antimicrobial agents with 92%

(n = 531) of infants receiving 940 antibiotics on the assessment day (Table 2), 19% (n = 108) receiving 108 antifungal agents, and 4% (n = 25) received 25 antiviral medications.

3.2. Antibacterial therapy

The majority of infants (55%, 293/531) received an antibacterial agent(s) as empiric therapy for possible infection while 38% (n = 204/531) received antibiotic(s) for a specific infection-related diagnosis and 6% (n = 34/531) for prophylaxis. The most frequent reason for infants receiving antibiotics was for possible sepsis ("rule-out sepsis"; 32%; n = 168/531) with the majority (66%; n = 111) of these infants being ≥3 days of age (Fig. 2). The second most frequent reason was "culture-negative" sepsis/meningitis (16%; n = 87). Only 20% of infants received antibacterial therapy for culture-confirmed infection (15%; n = 80, culture-proven sepsis/meningitis; 4%; n = 21, culture-proven urinary tract infection (UTI); 1%; n = 5 had both; Table 3). The most common single organisms detected in blood were coagulase-negative staphylococci (n = 32; 29%) and *Klebsiella pneumoniae* (n = 24; 22%) while in urine, *Klebsiella* spp. (n = 12; 39%) and *Escherichia coli* (n = 7; 23% Table 3) were the most frequent pathogens. Other indications for antibacterial therapy were pneumonia/tracheitis (15%; n = 82), NEC (8%; n = 42), surgical site infection (4%; n = 23), and congenital syphilis (2%; n = 12).

Among the 531 infants who received antibacterial therapy, ampicillin (40%, n = 211), gentamicin (35%, n = 185), and amikacin (19%, n = 101) were most frequently prescribed (Table 2). Among the 38% (204/531) of infants on definitive antibacterial therapy, vancomycin (26%, n = 53), amikacin (n = 20%, n = 40), and meropenem (16%, n = 32) were the most prescribed agents. An additional 35 (17%) infants received third and fourth generation cephalosporins. Access antibiotics were used more frequently by Africa, South America, North America, and Central America while Europe and Asia used

Fig. 1. Map of the 29 countries that participated in the NO-More-AntibioticS and Resistance (NO-MAS-R) study, a point prevalence study of all infants in the neonatal intensive care unit (NICU) who received at least one antimicrobial agent on July 1, 2019, the birthday of Ignaz Semmelweiss, MD. Participating countries (number of NICUs; total number of infants on antimicrobial therapy) by level of income were: High income, Belgium (n = 1; 3), Canada (n = 2; 5), Chile (n = 4; 38), Finland (n = 1; 10), Greece (n = 1; 5), Israel (n = 2; 14), Italy (n = 13; 77), Japan (n = 3; 12), Netherlands (n = 1; 9), Oman (n = 1; 3), Panama (n = 1; 1), Spain (n = 5; 35), Sweden (n = 1; 4), United States (n = 15; 84); Middle-to-Low Income, Argentina (n = 2; 10), Brazil (n = 1; 13), China (n = 1; 21), Colombia (n = 12; 43), Costa Rica (n = 1; 5), Ecuador (n = 3; 12), Ghana (n = 1; 10), Guyana (n = 1; 9), Haiti (n = 1; 29), Iran (n = 1; 3), Lebanon (n = 1; 2), Mexico (n = 1; 8), Nigeria (n = 3; 43), Peru (n = 2; 14), South Africa (n = 2; 58).

Table 1
Characteristics and outcome of the 580 infants who received antimicrobial therapy in the neonatal intensive care unit on July 1, 2019.

	Infants in Neonatal Intensive Care Unit						Total
	<3 days old			≥3 days old			
Country income	Low-to-Middle Income	High-Income	Total	Low-to-Middle Income	High-Income	Total	
No. of infants	60 (60%)	40 (40%)	100 (17%)	220 (46%)	260 (54%)	480 (83%)	580
Birth weight (grams, IQR)	2680 (1720−3110)	2208 (1575−3078)	2400 (1680−3100)	2253, 1200−2914	1350, 800−2460	1680 (995−2771)	1800 (1060−2835)
≤1000	3 (50%)	3 (50%)	6/100 (6%)	23 (18%)	102 (82%)	125/477 (26%)	131/577 (23%)
1001−1500	5 (42%)	7 (58%)	12/100 (12%)	50 (54%)	43 (46%)	93/477 (20%)	105/577 (18%)
1501−2500	20 (63%)	12 (38%)	32/100 (32%)	54 (51%)	51 (49%)	105/477 (22%)	137/577 (24%)
≥2501	32 (64%)	18 (36%)	50/100 (50%)	91 (59%)	63 (41%)	154/477 (32%)	204/577 (35%)
Chronologic age (days, IQR)	1 (1−2)	1 (1−2)	1 (1−2)	10 (5−27)	21 (9−61)	16 (6−40)	11 (4−33)
Gestational age (weeks, IQR)	36 (32−39)	34 (31−37)	34 (32−38)	34 (30−36)	30 (26−36)	32 (27−37)	33 (28−37)
≤28 weeks	3 (33%)	6 (67%)	9/93 (10%)	38 (26%)	109 (74%)	147/474 (31%)	156/567 (28%)
29−33 weeks	14 (56%)	11 (44%)	25/93 (27%)	59 (50%)	58 (50%)	117/474 (25%)	142/567 (25%)
34−36 weeks	14 (54%)	12 (46%)	26/93 (28%)	39 (50%)	39 (50%)	78/474 (16%)	104/567 (18%)
≥37 weeks	22 (67%)	11 (33%)	33/93 (35%)	79 (60%)	53 (40%)	132/474 (28%)	165/567 (29%)
Sex, male	33 (63%)	19 (37%)	52 (52%)	132 (46%)	156 (54%)	288 (60%)	340 (59%)
Race/ethnicity							
White	1 (4%)	25 (96%)	26 (26%)	1 (1%)	138 (99%)	139 (29%)	165 (28%)
Black	29 (100%)	0	29 (29%)	106 (82%)	23 (18%)	129 (27%)	158 (27%)
Hispanic	16 (76%)	5 (24%)	21 (21%)	81 (64%)	45 (36%)	126 (26%)	147 (25%)
Asian	5 (50%)	5 (50%)	10 (10%)	12 (50%)	12 (50%)	24 (5%)	34 (6%)
Other	4 (57%)	3 (43%)	7 (7%)	14 (33%)	29 (67%)	43 (9%)	50 (9%)
Unknown	5 (71%)	2 (29%)	7 (7%)	6 (32%)	13 (68%)	19 (4%)	26 (4%)
MDRO colonization							
MRSA	0	0	0	1 (25%)	3 (75%)	4 (1%)	4 (1%)
VRE	0	0	0	0	1 (100%)	1 (1%)	1 (1%)
CRE	0	0	0	1 (100%)	0	1 (1%)	1 (1%)
ESBL-Enterobacteriaceae	0	0	0	7 (88%)	8 (12%)	15 (3%)	15 (3%)
Respiratory support							
None	26 (62%)	16 (38%)	42/91 (46%)	92 (56%)	71 (44%)	163/454 (36%)	204/545 (38%)
Any	27 (55%)	22 (45%)	49/91 (54%)	112 (38%)	179 (62%)	291/454 (64%)	340/545 (62%)
Nasal cannula	15 (94%)	1 (6%)	16 (18%)	45 (61%)	29 (39%)	74 (15%)	90 (17%)
CPAP	4 (29%)	10 (71%)	14 (15%)	29 (37%)	49 (63%)	78 (16%)	92 (16%)
Mechanical ventilation	8 (42%)	11 (58%)	19 (21%)	37 (28%)	94 (72%)	131 (27%)	150 (26%)
Tracheostomy	0	0	0 (0%)	1 (13%)	7 (88%)	8 (2%)	8 (1%)
Central venous catheter	8 (32%)	18 (72%)	26 (26%)	61 (29%)	151 (72%)	212 (44%)	238 (41%)
Urinary catheter	0	4 (100%)	4 (4%)	6 (19%)	25 (81%)	31 (6%)	35 (6%)
Probiotic	1 (25%)	3 (75%(	4 (4%)	4 (3%)	27 (87%)	31 (6%)	35 (6%)
Lactoferrin	0	1 (100%)	1 (1%)	0	8 (100%)	8 (2%)	9 (2%)
Acid suppression medication	4 (100%)	0	4 (4%)	11 (26%)	31 (74%)	42 (9%)	46 (8%)
Mortality-30 day	3 (60%)	2 (40%)	5 (5%)	13 (46%)	15 (54%)	28 (6%)	33 (6%)
Infection-related	1 (33%)	2 (67%)	3 (60%)	6 (55%)	5 (45%)	11 (39%)	14 (42%)

IQR, interquartile range; MDRO, multi-drug resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum beta-lactamase; CPAP, continuous positive airway pressure.

more Watch antibiotics. Reserve antibiotics were used only by Europe and South America (Fig. 3).

At the initial assessment, the planned length of treatment was reported in the medical record for 475 (89%) of the 531 infants on antibiotics. The planned length of therapy was indicated as indefinite (15%, *n* = 72), 1 to 3 days (24%, *n* = 113), 4 to 6 days (10%, *n* = 49), 7 days (23%, *n* = 109), 10 days (12%, *n* = 59), 14 days (10%, *n* = 48), 21 days (3%, *n* = 16), or 4 to 6 weeks (2%, *n* = 9) for planned length of antibiotic therapy. The final length of therapy was reported on 405 (85%) of the 475 infants when assessed on follow-up at 30 days. The actual length of therapy was 7 days (median; IQR, 5−12 days) overall, with infants who received definitive treatment receiving 10 days (median; IQR, 7−15 days). Final length of therapy for culture-positive and culture-negative infections without concomitant diagnosis of meningitis was 12 days (median; IQR, 8−14 days) and 7 days (median; IQR, 5−10 days), respectively. Length of therapy for pneumonia was 7 days (median; IQR, 5−10 days), for UTI was 7 days (median; IQR, 7−14 days), and for NEC, 9 days (median; IQR, 7−15 days).

Length of antibiotic therapy for any indication did not differ between NICUs with or without NICU-specific ASPs (7 days [median; IQR, 5−13 days] vs. 8 days [median; IQR, 5−12], respectively; *p* = 0.99) nor was it different between high or low-to-middle income countries (7 days [median, [IQR, 4−12 days] vs. 9 days [median, IQR 5−13], respectively; *p* = 0.29). Similarly, length of antibiotic therapy for definitive treatment did not differ between NICUs with or without NICU-specific ASPs (10 days [median; IQR, 7−14 days] vs. 12 days [median; IQR, 7−16 days], respectively; *p* = 0.50) or between high vs. low-to-middle income countries (10 days [median; IQR, 7−14 days] vs. 10 days [median; IQR, 7−15 days], respectively; *p* = 0.50) 7 (IQR, 6−12). For infants >72 h of age, duration of empiric therapy was 7 days (median; IQR, 5−10) and 10 days for definitive treatment (median; IQR, 7−14). Duration of therapy with antibacterial agents for prophylaxis among infants was 16 days (median; IQR, 7−56).

3.3. Antifungal therapy

Of the 108 infants who received antifungal agents (fluconazole [59%, *n* = 64], amphotericin B deoxycholate [19%, *n* = 21], nystatin [18%, *n* = 19], amphotericin B liposomal [2%, *n* = 2], caspofungin [1%, *n* = 1], unknown [1%, *n* = 1]), the main indication was prophylaxis (62%, *n* = 67). Of the remaining 41 infants who received antifungal therapy, "rule-out sepsis" (54%; *n* = 22), sepsis (17%; *n* = 7), and skin/ soft tissue infections (10%; *n* = 4) were the most common indications. Definitive antifungal treatment for culture-confirmed fungal infection consisted mainly of fluconazole and amphotericin B

Table 2

Antibacterial therapy (*n* = 940) provided to 531 (23%) of 2265 infants in the neonatal intensive care unit of 84 hospitals in 29 countries grouped by the World Health Organization AWaRe classification.*

	Infants in Neonatal Intensive Care Unit						Tot al
	Infants < 3 Days Old			Infants ≥ 3 Days Old			
Country income	Low-to-Middle Income	High-Income	Total	Low-to-Middle Income	High-Income	Total	
No. of infants	60 (61%)	39 (39%)	99 (19%)	206 (48%)	226 (52%)	432 (81%)	531
Antibiotic group:[1]							
Access group	104	69	173	234	212	446	619
Ampicillin/amoxicillin	44	26	70	82	62	144	214
Gentamicin	34	27	61	69	55	124	185
Amikacin	16	6	22	45	41	86	108
Amoxicillin/clavulanate or ampicillin/sulbactam	5	1	6	17	10	27	33
Metronidazole	0	1	1	5	15	20	21
Penicillin G	4	5	9	5	5	10	19
Cloxacillin/oxacillin/nafcillin	0	0	0	5	12	17	17
Cephalexin/cefazolin	1	1	2	1	4	5	7
Cefadroxil	0	0	0	0	5	5	5
Clindamycin	0	2	2	2	1	3	5
Trimethoprim-sulfamethoxazole	0	0	0	3	2	5	5
Watch Group	7	10	17	128	149	277	294
Vancomycin	0	1	1	24	55	79	80
Meropenem	0	0	0	21	29	50	50
Cefotaxime	2	0	2	28	8	36	38
Ceftazidime	1	1	2	11	12	23	25
Piperacillin-tazobactam	0	1	1	9	11	20	21
Cefuroxime	3	0	3	11	4	15	18
Cefepime	0	1	1	9	7	16	17
Piperacillin	0	4	4	0	6	6	10
Imipenem	0	0	0	4	1	5	5
Teicoplanin	0	0	0	0	5	5	5
Tobramycin	0	1	1	0	4	4	5
Ceftriaxone	0	0	0	3	1	4	4
Ciprofloxacin	1	0	1	1	2	3	4
Levofloxacin	0	0	0	4	0	4	4
Erythromycin	0	0	0	1	2	3	3
Azithromycin	0	0	0	1	1	2	2
Clarithromycin	0	0	0	1	0	1	1
Rifampin	0	1	1	0	1	1	2
Reserve Group	0	0	0	1	2	3	3
Linezolid	0	0	0	0	2	2	2
Aztreonam	0	0	0	1	0	1	1
Other Group	0	1	1	2	21	23	24
Isoniazid	0	0	0	0	1	1	1
Bacitracin	0	1	1	0	4	4	5
Mupirocin	0	0	0	0	2	2	2
Other	0	0	0	2	14	16	16

*Antibiotics were grouped by the AWaRE (Access, Watch, and Reserve) classification on the basis of the WHO Essential Medicines List for Children. The Access group contains narrower-spectrum antibiotics, the Watch group contains broader spectrum antibiotic classes, and the Reserve group consist of antibiotics reserved for multidrug resistant infections.
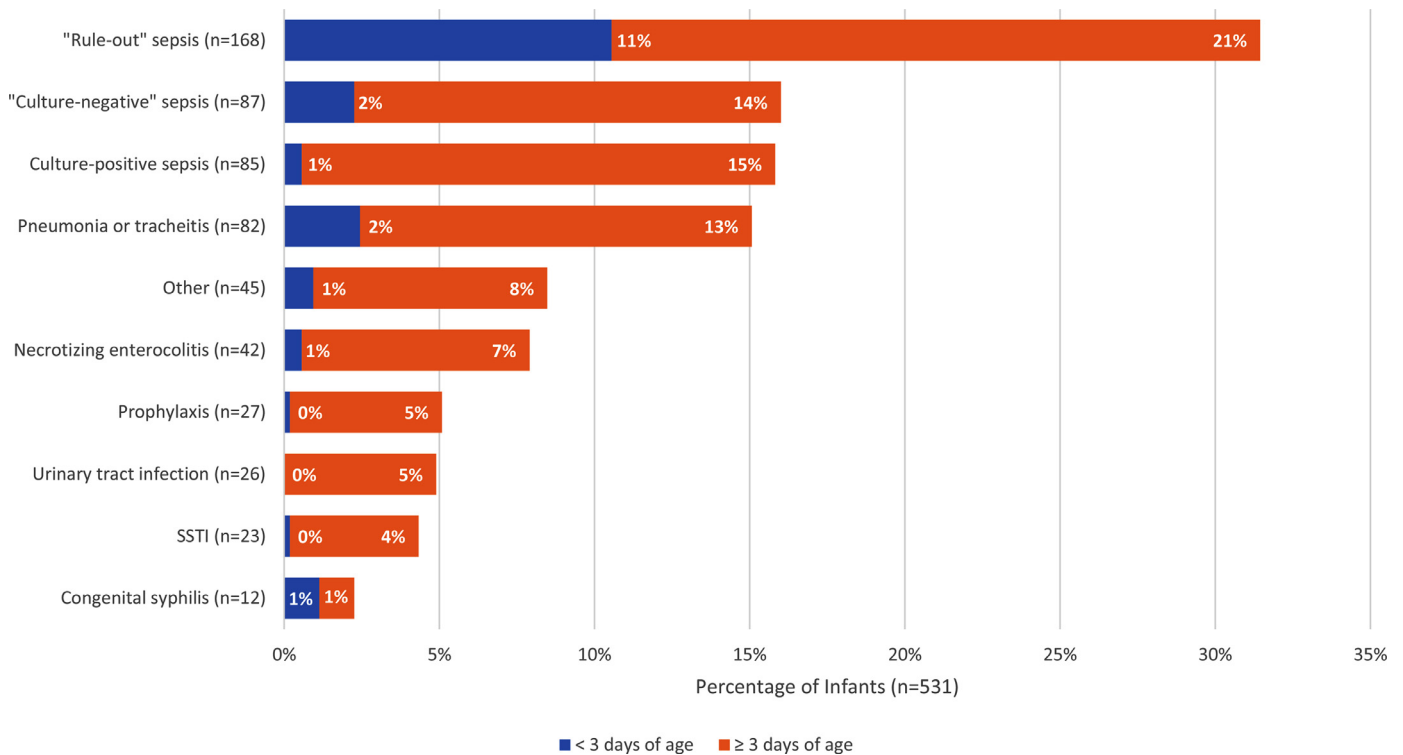
Fig. 2. Indications for antibiotic use among the 531 infants, with the percentage of infants who received antibacterial therapy for that indication on the x-axis.

deoxycholate therapy. Infants on definitive therapy with antifungal agents accounted for 17% (n = 18) of their use. Of the seven (n = 580; 1%) infants treated for systemic disease and had positive cultures for yeast (6, Candida spp. and 1 yeast not identified), 4 received fluconazole and 3 received amphotericin B deoxycholate. Of 67 patients who were on antifungal prophylaxis, the majority were extremely low birth weight infants, less than 1000 gs (69%; n = 46). Overall, 24 (29%) of the 84 hospital NICUs utilized fluconazole prophylaxis.

3.4. Antiviral therapy

Among the 25 infants who received antiviral agents, the main indication was prophylaxis (72%, n = 18) for exposure to maternal infection with human immunodeficiency virus and all received zidovudine monotherapy. Of the remaining seven infants, 5 received acyclovir (2, empiric; 3, treatment), 1 received ganciclovir for cytomegalovirus infection, and in one infant the specific antiviral agent was not known.

3.5. Other analyses

A hospital-wide ASP that included the NICU was present in 62% (n = 50/81) of hospitals (31 high-income and 19 low-to-middle income countries; p = 0·95). An NICU-specific ASP was present in 52% (40/77) of NICUs (23 high-income and 17 low-to-middle income countries; p = 0.47). Eight hospitals with NICU-specific ASP did not have a hospital-wide ASP. NICUs with their own ASP had significantly lower median rates of antibiotic utilization compared to those without one (18% vs. 29%, respectively; p-value=0.02). Similarly, these NICUs with ASP also had fewer antibiotic utilization per patient (1·4 vs. 1·7 antibiotics/patient) and used less Access antibiotics (0·89 vs. 1·2 antibiotic/patient) but similar Watch antibiotics (0·53 vs. 0·45 antibiotic/patient).

Eleven (2%) infants received probiotics and three had bloodstream infections with coagulase-negative staphylococci and two with Staphylococcus aureus, while one had NEC. Three (0·05%) infants

received lactoferrin and two had bloodstream infections with coagulase-negative staphylococci and one with S. aureus while the third had staphylococcal osteomyelitis. Among the 46 (8%) infants who received acid suppression medications, 14 had bloodstream infection (7, coagulase-negative staphylococci; 2, S. aureus; 3, Klebsiella pneumoniae; 1, Streptococcus pneumoniae; 1 polymicrobial with Stenotrophomonas maltophilia and coagulase-negative staphylococci).

3.6. Outcomes

Mortality at 30 days was 6% (33/580) and did not differ between infants who received antimicrobial agents in the first 48 h of age (5%; n = 5) versus those who were ≥72 h of age (6%; n = 28; Table 1). The percentage of deaths that were assessed as infection-related also was not different between the two groups (60% [3/5] vs. 39% [11/28], respectively). Of the 33 deaths, 42% (n = 14) were assessed as being related to infection.

4. Discussion

On July 1, 2019, 26% of high-risk infants in NICUs worldwide received at least one antimicrobial agent, mostly antibacterials and in those cared for in low-to-middle income countries. The majority of the infants received antibiotic therapy as empiric coverage for possible sepsis, although a substantial number were treated for "culture-negative" sepsis/meningitis and only a minority for culture-confirmed infection. Importantly, hospitals that had an NICU-specific ASP had significantly lower antibiotic utilization rates. The importance of such a program cannot be over-emphasized as it ultimately may help to decrease antimicrobial resistance in NICUs worldwide [34−46].

Infants often received antimicrobial therapy based on clinical suspicion of a serious bacterial infection rather than on positive bacterial culture results. After excluding antibiotics provided for prophylaxis and empiric therapy, 49% of infants received prolonged antibiotic therapy without microbiologic evidence of infection. The notion of

Table 3
Pathogens detected in blood and urine of the 580 infants who received antimicrobial therapy in the neonatal intensive care unit on July 1, 2019.

	Infants in Neonatal Intensive Care Unit						Total
	<3 Days Old			≥3 Days Old			
Country income	Low-to-Middle Income	High Income	Total	Low-to-Middle Income	High Income	Total	
No. of infants	60 (60%)	40 (40%)	100 (17%)	220	260	480 (83%)	580
No. of pathogens in blood:	3 (50%)	3 (50%)	6 (6%)	46	59	105 (22%)	111 (19%)
Gram-positive	2 (50%)	2 (50%)	4 (67%)	17	31	48 (46%)	52 (47%)
Coagulase-negative staphylococci (CoNS)*	0	2	2 (33%)	8	22	30 (29%)	32 (29%)
Streptococcus pneumoniae	0	0	0	8	0	8 (8%)	8 (7%)
Staphylococcus aureus	2	0	2 (33%)	1	4	5 (5%)	7 (6%)
Group B *Streptococcus*	0	0	0	0	2	2 (2%)	2 (2%)
Bacillus cereus	0	0	0	0	2	2 (2%)	2 (2%)
Enterococcus faecalis	0	0	0	0	1	1 (1%)	1 (1%)
Gram-negative	1	1	2 (33%)	23	20	43 (47%)	45 (41%)
Klebsiella spp*	1	0	1 (17%)	11	12	23 (22%)	24 (22%)
E. coli	0	1	1 (17%)	3	3	6 (6%)	7 (6%)
Pseudomonas aeruginosa	0	0	0	3	1	4 (4%)	4 (4%)
Enterobacter cloacae	0	0	0	1	2	3 (3%)	3 (3%)
Serratia marcescens	0	0	0	1	1	2 (2%)	2 (2%)
Acinetobacter species	0	0	0	2	0	2 (2%)	2 (2%)
Stenotrophomonas maltophilia	0	0	0	0	1	1 (1%)	1 (1%)
Pseudomonas fluorescens	0	0	0	1	0	1 (1%)	1 (1%)
Alcaligenes faecalis	0	0	0	1	0	1 (1%)	1 (1%)
Fungi	0	0	0	4	1	5 (%)	5 (5%)
Candida parapsilosis	0	0	0	2	1	3 (3%)	3 (3%)
Candida albicans	0	0	0	1	0	1 (1%)	1 (1%)
Yeast not identified	0	0	0	1	0	1 (1%)	1 (1%)
Polymicrobial	0	0	0	2	6	8 (8%)	8 (7%)
E. coli, CoNS	0	0	0	1	1	2 (2%)	2 (2%)
C. albicans, C. lusitaniae	0	0	0	0	1	1 (1%)	1 (1%)
S. maltophilia, CoNS	0	0	0	0	1	1 (1%)	1 (1%)
C. albicans, K. pneumoniae*	0	0	0	0	1	1 (1%)	1 (1%)
E. faecalis, K. pneumoniae	0	0	0	0	1	1 (1%)	1 (1%)
K. pneumoniae, P. aeruginosa, CoNS	0	0	0	0	1	1 (1%)	1 (1%)
B. pertussis, S. pneumoniae	0	0	0	1	0	1 (1%)	1 (1%)
Enterovirus*	0	0	0	0	1	1 (1%)	1 (1%)
No. of pathogens in urine	0	0	0	12	19	31 (6%)	31 (5%)
Gram-positive	0	0	0	0	1	1 (3%)	1 (3%)
Enterococcus spp.	0	0	0	0	1	1 (3%)	1 (3%)
Gram-negative	0	0	0	12	13	25 (81%)	25 (81%)
Klebsiella spp.	0	0	0	6	6	12 (39%)	12 (39%)
E. coli	0	0	0	3	4	7 (23%)	7 (23%)
Enterobacter spp.	0	0	0	0	3	3 (10%)	3 (10%)
P. aeruginosa	0	0	0	2	0	2 (6%)	2 (6%)
Gram negative bacilli, not yet identified	0	0	0	1	0	1 (3%)	1 (3%)
Fungi	0	0	0	0	1	1 (3%)	1 (3%)
C. albicans	0	0	0	0	1	1 (3%)	1 (3%)
Polymicrobial	0	0	0	0	4	4 (13%)	4 (13%)
Klebsiella. spp., *Enterococcus* spp., *S. aureus*	0	0	0	0	1	1 (3%)	1 (3%)
Klebsiella spp., *Enterococcus* spp.	0	0	0	0	1	1 (3%)	1 (3%)
E. coli, CoNS	0	0	0	0	1	1 (3%)	1 (3%)
E. coli, Enterococcus spp.	0	0	0	0	1	1 (3%)	1 (3%)

* Same pathogen also was detected in cerebrospinal fluid: 2, *Klebsiella pneumoniae*; 1, CoNS; 1, enterovirus
~Pathogens in polymicrobial cultures are not included in the listing of single isolates.

prolonged antibiotic therapy for "culture-negative" sepsis should be dispelled from our NICUs [47,48]. Infants in the NICU often experience prematurity-related events that mimic signs and symptoms of infection. Performance of full sepsis evaluations (e.g. blood, urine, cerebrospinal fluid) before initiation of antibiotic therapy, obtaining sufficient quantity of blood for culture, and investigation of viral and fungal etiologies should allow comfort in discontinuation of antibiotics if cultures are sterile [49−58]. Ultimately, genomic methods for detection of microbial pathogens in body fluids may allow optimal identification of infected infants and more appropriate use of antimicrobial therapy [59,60].

Overall length of antibiotic therapy was often prolonged (i.e., > 72 h) as 80% (325/405) of infants received a median of 7 days with definitive treatment for presumed or culture-positive infection being a median of 10 days. Final length of therapy for culture-positive and culture-negative infections without concomitant diagnosis of meningitis was 12 days (median; IQR, 8−14 days) and 7 days (median; IQR, 5−10 days), respectively. Although length of antibiotic therapy remains an unresolved issue, single center studies have suggested shorter courses of five total days are safe and effective for "culture-negative" sepsis and pneumonia [40,61−63]. Our study did not find any differences in length of therapy between centers irrespective of country, income level, or presence of ASP, confirming the need for robust research to address this knowledge gap.

Analysis of antibiotic use utilizing the WHO AWaRe classification revealed similar use of Access antibiotics across NICUs in South America, North America, and Central America, but higher Watch antibiotics in Europe and Asia (Fig. 3). As some broad spectrum agents such as meropenem are included in the Watch group, further assessment utilizing an antibiotic spectrum index may be a more optimal tool [30,64,65]. Overall use of Reserve antibiotics was low and these agents were only used in Europe and South America (Fig. 3).
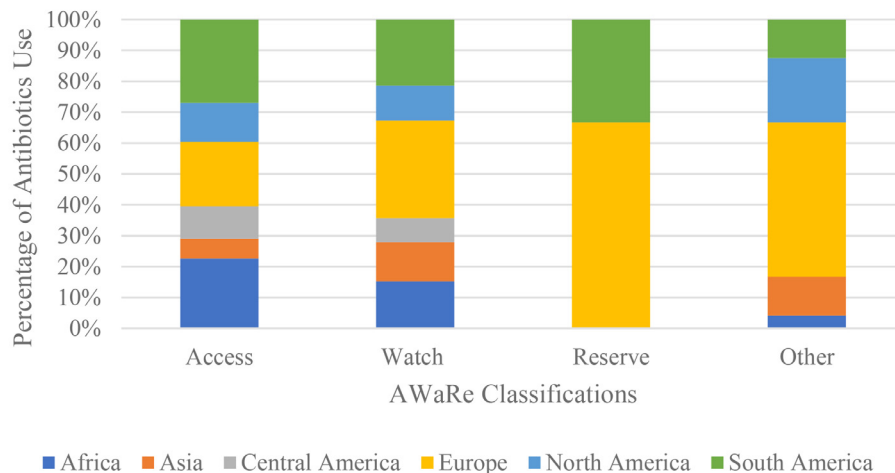
Fewer infants received antiviral agents in our study with the majority prescribed for HIV prophylaxis. Similarly, the majority of

Antibiotic Utilization by Global Region
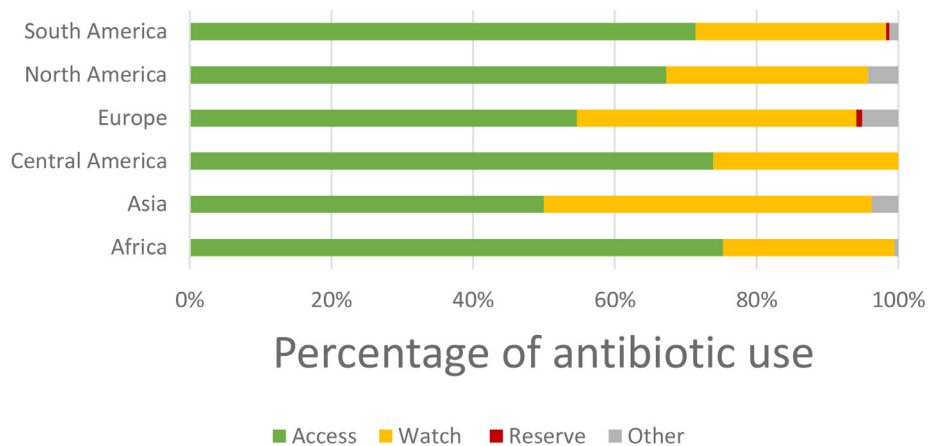
a)

Antibiotic Use Based on AWaRe Classification

b)

Fig. 3. Percentage of total antibiotic use among infants in the neonatal intensive care unit as determined by the World Health Organization AWaRe classification* by a) global region and b) AWaRe group. *AWaRe = Access, Watch, and Reserve.

antifungal agents were used for prophylaxis, although it varied by center as only 29% of NICUs utilized prophylactic fluconazole. The majority of treatment courses were for oral candidiasis, and only 1% (7/580) of infants were treated for systemic disease with either amphotericin B deoxycholate (*n* = 3) or fluconazole (*n* = 4). A more targeted assessment of antifungal prophylaxis and treatment is needed to address needed stewardship in this area [66].

Our novel, single-day, cross-sectional study has limitations. First of all and inherent in its design, a single-day prevalence study did not allow assessment of day-to-day variability or longitudinal trends, and thus the resulting wide uncertainty in antimicrobial use was demonstrated by the large range (0−100%) of infants exposed to antimicrobial agents in the 84 NICUs. The generalizability of the results was limited by 48% of the NICUs being from three countries, namely Colombia, Italy, and the United States. Recruitment of study sites was a convenient sample done through personal contact with individuals and centers, many of which have a specific interest in neonatal infectious diseases. It is therefore possible that our study may underestimate the actual use of antimicrobials globally especially among centers not devoted to antimicrobial stewardship. Similar studies

performed at a national level in Greece and Australia showed higher prevalence of antimicrobial use that ranged from 40% to 46%, respectively [19,22]. We also did not conduct personal interviews with prescribers to fully understand the rationale for initial and continuation of antimicrobial use beyond what was stated in the infant's medical record. Specific antibiotic mean inhibitory concentrations for detected pathogens also was not obtained in order to optimally assess use of more broad-spectrum agents in the Watch and Reserve groups. We did not query sites concerning antibiotic shortages or supply that could have influenced the type of antimicrobial agent(s) used. Finally, the proportion of infants who received probiotics and lactoferrin could not be ascertained since the number of infants who received them without receiving antimicrobial agents was not obtained.

In conclusion, we found that more than a quarter of infants in NICUs globally received at least one antimicrobial agent. Although the antibiotic utilization was lower in high-income countries, centers that had an NICU-specific ASP had lower antibiotic utilization rates regardless of the country's income level. The finding that NICU-specific ASP had a positive impact on utilization highlights the potential

value of such a program to reduce antibiotic consumption and possibly minimize the adverse effects associated with dysbiosis in high-risk infants.

Data sharing

All data will be available upon reasonable request to the corresponding author, and it will be shared according to the standards of ethical policies regulating data sharing of human subjects.

Authors' contributions

Pavel Prusakov (PP), Debra A. Goff, and Pablo J. Sánchez (PJS) conceptualized and designed the study and analyzed the data set. PP wrote the first draft of the manuscript. All authors are members of the Global NEO-ASP Study Group and obtained the local data, contributed to the interpretation of the data, and made critical revision of the manuscript for important intellectual content. All authors have read and agreed to the final version of the manuscript. PJS as the corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100727.

References

[1] Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin Jr. DK, Smith PB, et al. Medication use in the neonatal intensive care unit. Am J Perinatol 2014;31 (9):811–21.

[2] Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR, et al. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J 2005;24(9):766–73.

[3] Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017;390(10104):1770–80.

[4] Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med 2015;372(4):331–40.

[5] Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sanchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009;123(1):58–66.

[6] Alexander VN, Northrup V, Bizzarro MJ. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J Pediatr 2011;159 (3):392–7.

[7] Cantey JB, Pyle AK, Wozniak PS, Hynan LS, Sanchez PJ. Early antibiotic exposure and adverse outcomes in preterm, very low birth weight infants. J Pediatr 2018;203:62–7.

[8] Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr 2011;159(5):720–5.

[9] Novitsky A, Tuttle D, Locke RG, Saiman L, Mackley A, Paul DA. Prolonged early antibiotic use and bronchopulmonary dysplasia in very low birth weight infants. Am J Perinatol 2015;32(1):43–8.

[10] Ting JY, Roberts A, Sherlock R, Ojah C, Cieslak Z, Dunn M, et al. Duration of initial empirical antibiotic therapy and outcomes in very low birth weight infants. Pediatrics 2019;143(3).

[11] Ting JY, Synnes A, Roberts A, Deshpandey A, Dow K, Yoon EW, et al. Association between antibiotic use and neonatal mortality and morbidities in very low-birth-weight infants without culture-proven sepsis or necrotizing enterocolitis. JAMA Pediatr 2018;170(12):1181–7.

[12] Ting JY, Synnes A, Roberts A, Deshpandey AC, Dow K, Yang J, et al. Association of antibiotic utilization and neurodevelopmental outcomes among extremely low gestational age neonates without proven sepsis or necrotizing enterocolitis. Am J Perinatol 2018;35(10):972–8.

[13] Cantey JB, Huffman LW, Subramanian A, Marshall AS, Ballard AR, Lefevre C, et al. Antibiotic exposure and risk for death or bronchopulmonary dysplasia in very low birth weight infants. J Pediatr 2017;181:289–93.

[14] de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. Lancet 2000;355(9208):973–8.

[15] Johnston KJ, Thorpe KE, Jacob JT, Murphy DJ. The incremental cost of infections associated with multidrug-resistant organisms in the inpatient hospital setting-A national estimate. Health Serv Res 2019;54(4):782–92.

[16] Schulman J, Benitz WE, Profit J, Lee HC, Duenas G, Bennett MV, et al. Newborn antibiotic exposures and association with proven bloodstream infection. Pediatrics 2019;144(5).

[17] Schulman J, Profit J, Lee HC, Duenas G, Bennett MV, Parucha J, et al. Variations in neonatal antibiotic use. Pediatrics 2018;142(3).

[18] Cantey JB, Wozniak PS, Sanchez PJ. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. Pediatr Infect Dis J 2015;34(3):267–72.

[19] Osowicki J, Gwee A, Noronha J, Britton PN, Isaacs D, Lai TB, et al. Australia-wide point prevalence survey of antimicrobial prescribing in neonatal units: how much and how good? Pediatr Infect Dis J 2015;34(8):e185–90.

[20] Versporten A, Sharland M, Bielicki J, Drapier N, Vankerckhoven V, Goossens H, et al. The antibiotic resistance and prescribing in European Children project: a neonatal and pediatric antimicrobial web-based point prevalence survey in 73 hospitals worldwide. Pediatr Infect Dis J 2013;32(6):e242–53.

[21] Hsia Y, Lee BR, Versporten A, Yang Y, Bielicki J, Jackson C, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Health 2019;7(7):e861–e71.

[22] Gkentzi D, Kortsalioudaki C, Cailes BC, Zaoutis T, Kopsidas J, Tsolia M, et al. Epidemiology of infections and antimicrobial use in Greek Neonatal Units. Arch Dis Child Fetal Neonatal Ed 2019;104(3):F293–F7.

[23] Shipp KD, Chiang T, Karasick S, Quick K, Nguyen ST, Cantey JB. Antibiotic stewardship challenges in a referral neonatal intensive care unit. Am J Perinatol 2016;33(5):518–24.

[24] Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, et al. The worldwide antibiotic resistance and prescribing in European children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother 2016;71(4):1106–17.

[25] Citrome L. Happy birthday ignac semmelweiss! now, let's all wash our hands!. Int J Clin Pract 2018;72(10):e13256.

[26] American Academy of Pediatrics Committee on F. Newborn. Levels of neonatal care. Pediatrics 2012;130(3):587–97.

[27] Krumholz HM, Normand SL. Public reporting of 30-day mortality for patients hospitalized with acute myocardial infarction and heart failure. Circulation 2008;118(13):1394–7.

[28] Scott HF, Brou L, Deakyne SJ, Kempe A, Fairclough DL, Bajaj L. Association between early lactate levels and 30-day mortality in clinically suspected sepsis in children. JAMA Pediatr 2017;171(3):249–55.

[29] WHO. The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use. Geneva: World Health Organization; 2019 WHO/EMP/IAU/2019.11). . 2019.

[30] Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use-be AWaRe. Lancet Infect Dis 2018;18(1):18–20.

[31] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.

[32] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.

[33] Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. Annu Rev Public Health 2002;23:151–69.

[34] Araujo da Silva AR, Marques A, Di Biase C, Faitanin M, Murni I, Dramowski A, et al. Effectiveness of antimicrobial stewardship programmes in neonatology: a systematic review. Arch Dis Child 2020;105(6):563–8.

[35] Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. Infect Dis Clin North Am 2014;28(2):247–61.

[36] Dukhovny D, Buus-Frank ME, Edwards EM, Ho T, Morrow KA, Srinivasan A, et al. A collaborative multicenter QI initiative to improve antibiotic stewardship in newborns. Pediatrics 2019;144(6).

[37] Johnson CL, Saiman L. A blueprint for targeted antimicrobial stewardship in neonatal intensive care units. Infect Control Hosp Epidemiol 2017;38(10):1144–6.

[38] Cantey JB. Optimizing the use of antibacterial agents in the neonatal period. Paediatr Drugs 2016;18(2):109–22.

[39] Dramowski A, Velaphi S, Reubenson G, Bekker A, Perovic O, Finlayson H, et al. National neonatal sepsis task force launch: supporting infection prevention and surveillance, outbreak investigation and antimicrobial stewardship in neonatal units in South Africa. S Afr Med J 2020;110(5):360–3.

[40] McCarthy KN, Hawke A, Dempsey EM. Antimicrobial stewardship in the neonatal unit reduces antibiotic exposure. Acta Paediatr 2018;107(10):1716–21.

[41] Rueda MS, Calderon-Anyosa R, Gonzales J, Turin CG, Zea-Vera A, Zegarra J, et al. Antibiotic overuse in premature low birth weight infants in a developing country. Pediatr Infect Dis J 2019;38(3):302–7.

[42] Sanchez PJ, Moallem M, Cantey JB, Milton A, Michelow IC. Empiric therapy with vancomycin in the neonatal intensive care unit: let's "get smart" globally!. J Pediatr (Rio J) 2016;92(5):432–5.

[43] Steinmann KE, Lehnick D, Buettcher M, Schwendener-Scholl K, Daetwyler K, Fontana M, et al. Impact of empowering leadership on antimicrobial stewardship: a single center study in a neonatal and pediatric intensive care unit and a literature review. Front Pediatr 2018;6:294.

[44] Ting JY, Shah PS. Antibiotic stewardship in neonates: challenges and opportunities. Transl Pediatr 2020;9(3):198–201.

[45] Ting JY, Paquette V, Ng K, Lisonkova S, Hait V, Shivanada S, et al. Reduction of inappropriate antimicrobial prescriptions in a tertiary neonatal intensive care unit after antimicrobial stewardship care bundle implementation. Pediatr Infect Dis J 2019;38(1):54–9.

[46] Urzua S, Ferres M, Garcia P, Sanchez A, Luco M. Strategies to reduce infections and antibiotic use and its effects in a neonatal care unit. Rev Chilena Infectol 2017;34(2):99–107.

[47] Cantey JB, Sanchez PJ. Prolonged antibiotic therapy for "culture-negative" sepsis in preterm infants: it's time to stop!. J Pediatr 2011;159(5):707–8.

[48] Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal ICU. Pediatrics 2017;140(4).

[49] Moallem M, Song E, Jaggi P, Conces MR, Kajon AE, Sanchez PJ. Adenovirus and "culture-negative sepsis" in a preterm neonate. AJP Rep 2016;6(4):e417–e20.

[50] Ronchi A, Doern C, Brock E, Pugni L, Sanchez PJ. Neonatal adenoviral infection: a seventeen year experience and review of the literature. J Pediatr 2014;164(3):529–35 e1-4.

[51] Ronchi A, Michelow IC, Chapin KC, Bliss JM, Pugni L, Mosca F, et al. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. J Pediatr 2014;165(4):690–6.

[52] Ronchi A, Ouellette CP, Mejias A, Salamon D, Leber A, Pugni L, et al. Detection of cytomegalovirus in saliva from infants undergoing sepsis evaluation in the neonatal intensive care unit: the VIRIoN-C study. J Perinat Med 2018;47(1):90–8.

[53] Lanzieri TM, Dollard SC, Josephson CD, Schmid DS, Bialek SR. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. Pediatrics 2013;131(6):e1937–45.

[54] Bennett NJ, Tabarani CM, Bartholoma NM, Wang D, Huang D, Riddell SW, et al. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal intensive care units. J Pediatr 2012;161(5):814–8.

[55] Cantey JB. The spartacus problem: diagnostic inefficiency of neonatal sepsis. Pediatrics 2019;144(5).

[56] Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-negative early-onset neonatal sepsis - at the crossroad between efficient sepsis care and antimicrobial stewardship. Front Pediatr 2018;6:285.

[57] Lamba V, D'Souza S, Carafa C, Zepf A, Bassel CL, Gutierrez M, et al. Standardizing the approach to late onset sepsis in neonates through antimicrobial stewardship: a quality improvement initiative. J Perinatol 2020.

[58] Ho T, Buus-Frank ME, Edwards EM, Morrow KA, Ferrelli K, Srinivasan A, et al. Adherence of newborn-specific antibiotic stewardship programs to CDC recommendations. Pediatrics 2018;142(6).

[59] Blauwkamp TA, Thair S, Rosen MJ, Blair L, Lindner MS, Vilfan ID, et al. Analytical and clinical validation of a microbial cell-free DNA sequencing test for infectious disease. Nat Microbiol 2019;4(4):663–74.

[60] Witt RG, Blair L, Frascoli M, Rosen MJ, Nguyen QH, Bercovici S, et al. Detection of microbial cell-free DNA in maternal and umbilical cord plasma in patients with chorioamnionitis using next generation sequencing. PLoS ONE 2020;15(4):e0231239.

[61] Engle WD, Jackson GL, Sendelbach D, Ford D, Olesen B, Burton KM, et al. Neonatal pneumonia: comparison of 4vs 7 days of antibiotic therapy in term and near-term infants. J Perinatol 2000;20(7):421–6.

[62] Engle WD, Jackson GL, Sendelbach DM, Stehel EK, Ford DM, McHugh KM, et al. Pneumonia in term neonates: laboratory studies and duration of antibiotic therapy. J Perinatol 2003;23(5):372–7.

[63] Cantey JB, Wozniak PS, Pruszynski JE, Sanchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis 2016;16(10):1178–84.

[64] Lahart AC, McPherson CC, Gerber JS, Warner BB, Lee BR, Newland JG. Application of an antibiotic spectrum index in the neonatal intensive care unit. Infect Control Hosp Epidemiol 2019;40(10):1181–3.

[65] Gerber JS, Hersh AL, Kronman MP, Newland JG, Ross RK, Metjian TA. Development and application of an antibiotic spectrum index for benchmarking antibiotic selection patterns across hospitals. Infect Control Hosp Epidemiol 2017;38(8):993–7.

[66] Johnson MD, Lewis RE, Dodds Ashley ES, Ostrosky-Zeichner L, Zaoutis T, Thompson GR, et al. Core recommendations for antifungal stewardship: a statement of the mycoses study group education and research consortium. J Infect Dis 2020;222(Supplement_3):S175–S98.