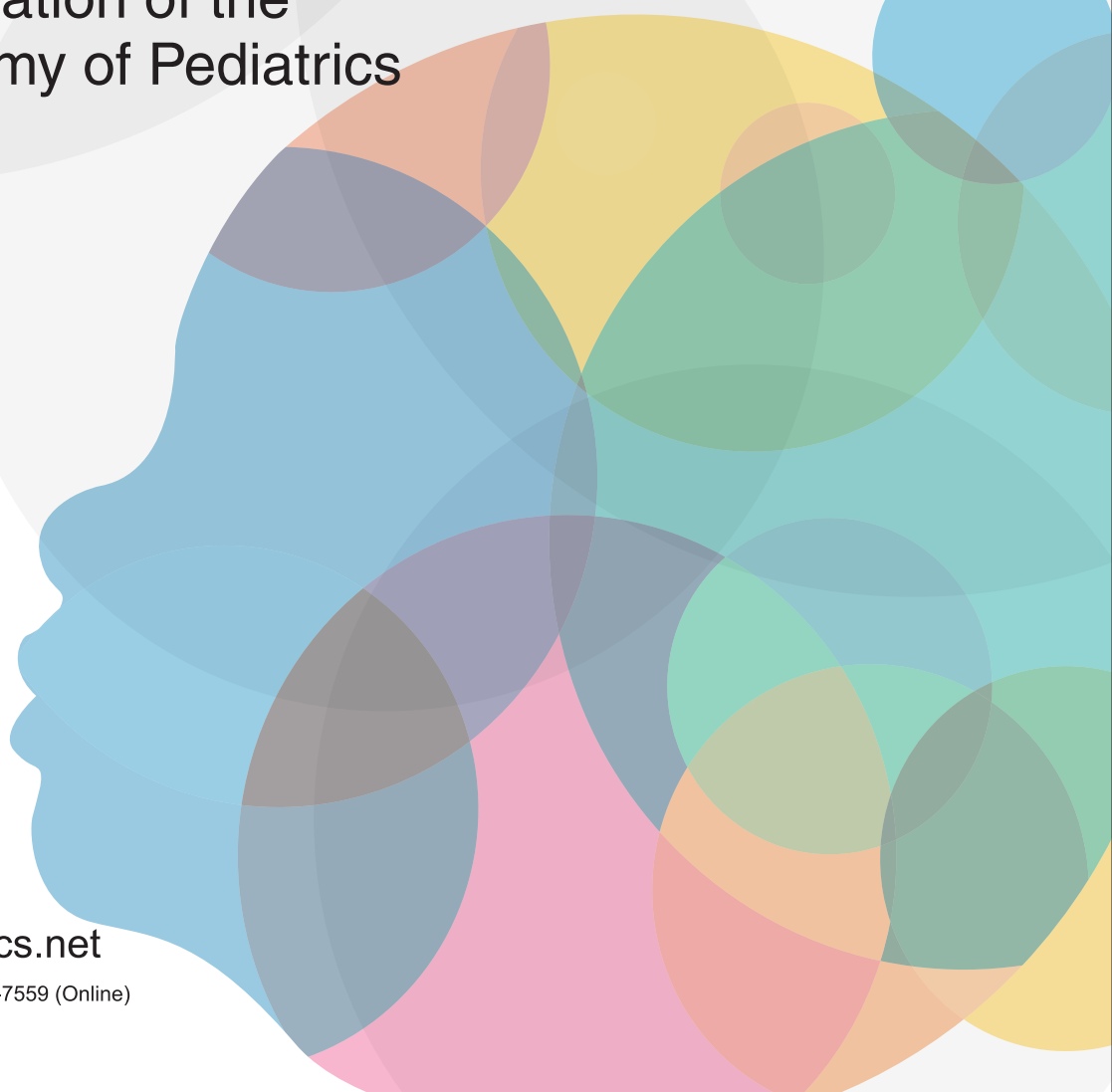
E-copy

Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

VOLUME 58
NUMBER 04
APRIL 2021



www.indianpediatrics.net

ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

Polybion® Lc

Vitamin B_1, Vitamin B_6, Vitamin B_{12} & Lysine Syrup

- Stimulates Appetite[1]
- Supports Immunity[1]
- Aids energy release[2]

Tasty Mango Flavour

India's NO. 1 B-Complex*

MAT-IN-OTHER-20-000119

*Polybion is India's largest selling brand by Qty Sales on MAT basis in the Vitamin B complex Liquid market as per IQVIA SSA Jul'20 dataset. Source: IQVIA Copyright 2020 All rights reserved.

Ref: 1. EFSA Journal 2011;9(4):2063
2. Laquale, Kathleen M (2006). B-complex vitamins' role in energy release. In Movement Arts, Health Promotion and Leisure Studies Faculty Publications. Paper 25.

Indian Pediatrics

April 2021 | Volume 58 | Number 4

Contents

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 31,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net.* There are no charges for publishing in the journal.

Address for ordinary letters: **The Editor-in-Chief, Indian Pediatrics, P. Box No. 3889, New Delhi-110 049, India.**
Address for registered/speed post letters: **Dr. Devendra Mishra, Editor-in-Chief, Indian Pediatrics, 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049, India. Tel: (011) 46052593**
E-mail: *jiap@nic.in*; Website: *www.indianpediatrics.net*; Facebook: *www.facebook.com/Indianpediatrics;* Twitter: *@EditorIndPed;* Instagram: *@indianpediatrics*

India's Universal Mega-dose Vitamin A Supplement Program: Time to Bid Goodbye!

PIYUSH GUPTA

Professor and Head, Department of Pediatrics, University College of Medical Sciences, Delhi, India. president@iap.org.in

Mega-dose vitamin A supplementation (MDVAS) was initiated by the Govt. of India in 1970 as a stop gap arrangement to tackle the issue of clinical vitamin A deficiency, resulting in childhood blindness. Half-a-century later, the program continues as such, without any re-evaluation. All under-five children are being administered 9 mega doses of vitamin A with first dose starting from 9 months of age, followed by two doses every year between 1-5 years.

Started primarily for decreasing the prevalence of xerophthalmia, the program was taken up by the World Health Organization (WHO) and promoted and projected to reduce the overall child morbidity and mortality in settings where vitamin A deficiency was recognized as a public health problem. However, massive reduction in clinical signs of vitamin A deficiency, improved diets, substantial declines in under-five mortality, and lack of consistent evidence of survival benefit in the Indian context have prompted an urgent evidence-based relook at the wisdom of continuing this program [1].

WHO defines vitamin A deficiency as a significant public health problem, when the prevalence of night blindness is >1% in children between 2-5 years and/or the serum retinol levels are below 20 μg/dL in ≤20% of children aged 6-59 months [2]. The recent Comprehensive National Nutrition Survey (CNNS; 2016-18) conducted in 30 states has shown the prevalence of vitamin A deficiency (VAD; defined as serum retinol <20 μg/dL) in 1-4 year old children as 15.7% (95% CI 15.2%, 16.3%), after adjusting for inflammation (objectively measured by elevated levels of C-reactive protein). There was no urban/rural or sex differences in prevalence. Also, the VAD prevalence was below 20% at the National level, irrespective of whether the children had received MDVAS in the past 6 months [3]. This definitely proved the point that vitamin A supplementation under programmatic circumstances had negligible role in increasing serum retinol concentration.

Looking at the state-wise data, only Jharkhand, Mizoram and Telangana qualified as states having the lower 95% CI of VAD prevalence above 20%. Add to these the states where the lower CI could be <20%, but the point prevalence was >20%, these included Bihar, Haryana, Madhya Pradesh, and Uttar Pradesh. It appears logical that except these seven states, the universal MDVAS can be safely discontinued in other areas. There are also five union territories for which serum retinol data are not available i.e., Andaman Nicobar Island, Chandigarh, Lakshadweep, Puducherry and Dadra Nagar Haveli, and Daman and Diu. Decisions on these can be taken based on experience and data of states which are geographically and culturally closest. Another issue worth considering is reduction of ongoing 9 doses to 5 doses (i.e. up to 3 years of age) in areas targeted for MDVAS.

It is important to note that the CNNS survey was performed before the regulations on the mandatory vitamin A fortification of cooking oil and the voluntary vitamin A fortification of milk were notified by the Indian government in 2018 [4]. The risk of excessive vitamin A intake related harm, from multiple vitamin A interventions coupled with dietary intakes, is now real and needs to be mitigated. Accounting for the potential acute toxicity of MDVAS, the campaign mode (i.e. the biannual round) administration needs to be stopped altogether.

Reduction in all cause child mortality, mediated by vitamin A supplementation, should be analyzed for the intended target population. A meta-analysis of 5 studies of MDVAS conducted in India and its effect on mortality showed no significant survival benefit [5], in contrast to the Cochrane analysis of global evidence that included much older trials when vitamin A deficiency was rife [6]. Further, considering the current 6 months to 5-year mortality rate in India, even the estimated 12% mortality reduction from the meta-analysis of global trials has no practical relevance, especially with suboptimal programmatic coverage [5]. The current under-five mortality in India is mainly contributed by neonatal deaths, where there is no role of universal MDVAS, as it is started only after 6 month of age.

A valid concern is the availability of vitamin A following phasing out of MDVAS. It needs to be emphasized that vitamin A should remain an essential part of Essential Drug list for therapeutic use in measles, severe acute malnutrition, chronic liver disease, and persistent diarrhea.

Surveillance and monitoring for both mortality and ocular manifestations will remain the key gauge for success and safety of targeted intervention following withdrawal of MDVAS from several states. The strategy in targeted states will also need to be revisited after 3-4 years.

We need to understand that there are no magical solutions or quick fixes for achieving permanency of positive outcomes. Long-term solutions to public health problems need to consistently aim at improving our health care delivery infrastructure, promoting living conditions, holistic approaches, and sustainable food-based solutions.

Competing interests: None declared.
Funding: None.

REFERENCES

1. Greiner T, Mason J, Benn CS, Sachdev HPS. Does India need a universal high-dose vitamin a supplementation program? Indian J Pediatr. 2019;86:538-41.
2. WHO Guideline. Vitamin A supplementation in infants and children 6-59 months of age. Geneva: WHO; 2011.
3. Comprehensive National Nutrition Survey (CNNS). Ministry of Health and Family Welfare (MoHFW), Government of India, UNICEF and Population Council. 2019.
4. National Report. New Delhi. Food Safety and Standards Authority of India (FSSAI). Gazette of India: Notification, Part-2: standards on fortification. Ministry of Health and Family Welfare; 2018.
5. Reddy GB, Pullakhandam R, Ghosh S, et al. Vitamin A deficiency among children younger than 5 y in India: An analysis of national data sets to reflect on the need for vitamin A supplementation. Am J Clin Nutr. 2020. Dec 16:nqaa314.
6. Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. Cochrane Database Syst Rev. 2017;3:CD008524.

EDITORIAL COMMENTARY

Focusing on Operational Research: A Welcome Step!

DHEERAJ SHAH

Department of Pediatrics, University College of Medical Sciences & GTB Hospital, Dilshad Garden, Delhi 110095, India.
shahdheeraj@hotmail.com

Over the last decade, India has made substantial progress in child health, particularly in terms of improvement of health services during pregnancy and delivery, widespread provision of facility based neonatal care, and better treatment of common childhood diseases – leading to a reduction in infant mortality rate (IMR) by almost 40% and under 5 mortality rate by 45% [1]. However, there is still much work to be done as regional and socioeconomic inequalities still exist, preventable conditions such as neonatal asphyxia, neonatal sepsis, pneumonia and diarrhea are still the most common causes of under 5 deaths [2], and malnutrition is the major risk factor underlying these deaths [3]. Moreover, with better survival, we must now focus on quality and productivity of life.

Medical research and innovations have played an important role in reducing the impact of greatest health problems faced by children. When interventions that are proved to be efficacious in research settings are delivered to the communities, the impact is very often diluted due to unique challenges in the health systems. Understanding the magnitude of these challenges, their possible causes, and providing customized solutions is extremely important, particularly in low- and middle-income country (LMIC) settings with high disease burden, socio-economic and cultural inequalities, and limited resources and time. In such settings, investment in operational research results in huge payoffs, and becomes more important than basic research. However, there is a dearth of operational research in our country, not only in terms of quantity of literature, but also the capacity and intent.

Operational research has its roots in military and economics, where it plays a vital role in increasing managerial productivity and resource management. In health perspective, operational research is defined as "the search for knowledge on interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programmes in which the research is being done [4]." The main features which distinguish operational research from other kind of research are: (*i*) that the research is conducted in real life settings, and not in controlled research settings; and (*ii*) there is an intention and plan to use the research findings to solve the programs related to implementation and improving healthcare delivery [5]. Operational research enables decision-makers to improve the performance of health programs through identification of problems that limit program outputs, quality and efficiency, finding their solutions, and trying alternative strategies by optimizing program outputs and processes for improved outcomes [6].

In India, like in most other LMICs, a large majority of the research published in peer review journals is generated by researchers from academic institutions. These publications are predominantly based on topics from basic or clinical sciences, or questions of efficacy of interventions. There is no doubt that such research has important role to play in advancement of science, but for the country's needs, these need to be supplemented by operational research through partnerships. It is heartening to see five research papers predominantly catering to operational/implementation issues in this issue of *Indian Pediatrics* [7-11]. This series of publications has emanated from research carried out through Norway-India Partnership Initiative in 13 selected districts of four of the Empowered action group (EAG) states that contribute to maximum child mortality (Bihar, Madhya Pradesh, Odisha and Rajasthan). In one of these papers, authors have assessed childhood diarrhea and pneumonia management practices, and highlighted important gaps in terms shortage of staff, problems with availability and utilization of drugs and equipments, and suboptimal treatment practices (e.g. irrational use of antibiotics, excessive use of intravenous fluids, underutilization of ORS) [7]. Authors suggested several possible solutions, including establishment of triage systems, skill enhancement in emergency and facility-based management of childhood illnesses, and standardization of patient record formats. In another interesting paper from this group [8], more than 6000 neonates discharged from Special newborn care units (SNCUs) of these districts were followed-up at community level till six weeks of life. A relatively high rate of mortality

(1.5%) and high re-referral rate (11% at every visit) were noted in the discharged neonates with the risk for mortality being five times higher for low birth weight neonates (2% vs. 0.4%). This calls for establishment of better continuum of care services for neonates discharged from SNCUs, especially for those with low birth weight. Regarding performance parameters during inpatient stay of neonates, it was noted that 36 out of 38 SNCUs were conducting family participatory care (FPC) sessions, and majority were providing support to mothers on FPC, and assistance related to breastfeeding and kangaroo mother care [9]. The barriers to optimal performance were also recorded, but it would have been better if such exercise was done following proper qualitative methods so that results could be utilized directly to improve performance parameters in some of these facilities. In another study [10], authors analyzed weight records of over 350,000 infants born over a 2-year period, through over 2.5 million home visits carried out by health workers during first year of their birth. These are huge datasets, which could be analyzed in more details leading to better understanding of the causes and consequence of undernutrition among children in these districts. In the last of the paper from this group, authors utilized online databases from SNCUs to develop a Quality of care index, and pilot tested the same in SNCUs in Rajasthan and Odisha [11]. In a publication elsewhere, authors subsequently used this score in non-EAG states, and reported it to be usable and doable [12].

These publications have served important role in identifying several problems (and their reasons with possible solutions) related to newborn and child health in selected districts of EAG states with high child mortality. However, as highlighted earlier, the concept of operational research must have an inbuilt mechanism of directly utilizing the knowledge and experience gained from research for improving healthcare delivery. It is important to ensure that these findings do not remain on paper as a routine monitoring and evaluation exercise, but are translated into benefit to the children and their families in these or similar settings. It is understandable that such benefits might not occur in short-term as the processes leading to re-implementation of improved strategies are often complex and iterative [4]. Simultaneously, similar operational research on widespread scale is the need of the hour in order to further improve the child health indicators of the country with best utilization of meager resources, especially in present era when health systems as well as resources are compromised by the ongoing COVID pandemic. There is a strong case to build capacity of researchers in carrying out operational research through partnerships of academic institutions, non-governmental organizations, policy makers and government agencies so that research outcomes feed the policy and improve outcomes for the children of the country. *Indian Pediatrics* has always taken the lead on issues related to child health, and has rightly nailed the focus on operational research, which is definitely the need of the hour.

Funding: None; *Competing interest:* None stated.

REFERENCES

1. UNICEF Data: Monitoring the Situation of Children and Women: India – Key Demographic Indicators. Accessed March 07, 2021. Available from: *https:// data.unicef.org/ country/ind/*
2. Million Death Study Collaborators. Changes in cause-specific neonatal and 1-59-month child mortality in India from 2000 to 2015: A nationally representative survey. Lancet. 2017;390:1972-80.
3. India State-Level Disease Burden Initiative Malnutrition Collaborators. The burden of child and maternal malnutrition and trends in its indicators in the states of India: the Global Burden of Disease Study 1990-2017. Lancet Child Adolesc Health. 2019 ;3:855-70.
4. Zachariah R, Harries AD, Ishikawa N, et al. Operational research in low-income countries: What, why, and how? Lancet Infect Dis. 2009;9:711-7.
5. Kumar AM, Harries AD, Satyanarayana S, Thekkur P, Shewade HD, Zachariah R. What is operational research and how can national tuberculosis programmes in low- and middle-income countries use it to end TB? Indian J Tuberc. 2020;67 (Suppl 2):S23-32.
6. World Health Organization. Guide to Operational Research in Programs Supported by the Global Fund. Accessed March 07, 2021. Available from: *https://www.who.int/ hiv/ pub/operational/ or_guide_gf.pdf*
7. Kumar H, Bhat AA, Alwadhi V, et al. Situational analysis of management of childhood diarrhea and pneumonia in 13 district hospitals in India. Indian Pediatr. 2021; 58:332-37.
8. Kumar H, Bhat AA, Alwadhi V, et al. Special Newborn Care Plus Project in India: Preliminary findings from community based follow-up of newborns discharged from facilities. Indian Pediatr. 2021; 58:354-57.
9. Kumar H, Bhat AA, Alwadhi V, et al. An assessment of implementation of family participatory care in special newborn care units in three states of India. Indian Pediatr. 2021; 58:349-53.
10. Kumar H, Khanna R, Alwadhi V, et al. Tracking weight-for-age of infants using Home Based Newborn Care Plus by ASHA workers. Indian Pediatr. 2021; 58:345-48.
11. Kumar H, Khanna R, Alwadhi V, et al. Catalytic support for improving clinical care in Special Newborn Care Units (SNCU) through composite SNCU Quality of Care Index (SQCI). Indian Pediatr. 2021; 58:338-44.
12. Saboth PK, Sarin E, Alwadhi V, et al. Addressing quality of care in pediatric units using a digital tool: Implementation experience from 18 SNCU of India. J Trop Pediatr. 2021;67:fmab005.

PERSPECTIVE

E-cigarettes and Vaping: A Global Risk for Adolescents

SWATI Y BHAVE[1] AND NICHOLAS CHADI[2]

From [1]AACCI – Association of Adolescent and Child Care in India , Mumbai, India; and [2]Division of Adolescent Medicine, Department of Pediatrics, Sainte-Justine University Hospital Centre, Université de Montréal, Montreal, QC, Canada.

Correspondence to: Dr Swati Y Bhave, 601 Alliance Shanti, Shantisheela Co-operative society, Pune 411 004, Maharashtra, India. sybhave@gmail.com

While the marketing and sale of electronic cigarettes (e-cigarettes) in India is forbidden since September, 2019, vaping represents a significant risk to the health and safety of Indian adolescents. Though the prevalence of youth e-cigarette use in India remains unknown, pediatricians are often brought to provide care to youth who vape. In this commentary, background information on e-cigarettes including a review of the different types of vaping devices and of the substances contained in e-cigarette liquids is provided. The short- and long-term health risks associated with vaping, including risks for the developing brain, acute lung injuries and long-term mental health effects, and a practical approach for clinical management of e-cigarette use for Indian pediatricians is presented. Public health measures to prevent and reduce youth vaping and a review of current Indian laws and policies around e-cigarette use are also mentioned.

Keywords: *ENDS, Nicotine, Smoking, Substance use.*

In the span of less than a decade, electronic cigarettes, also called electronic nicotine delivery systems (ENDS), or e-cigarettes, have completely changed the landscape of nicotine product use among adolescents and young adults [1]. Initially introduced as a harm reduction and smoking cessation strategy for adult cigarette smokers, e-cigarettes and other vaping devices have rapidly become popular among youth around the world. Aggressive youth-directed marketing from e-cigarette companies, easy and widespread access to vaping products, low cost, low perceptions of risk, youth-friendly flavors and designs, as well as highly effective nicotine delivery leading to intense psychoactive effects are a few reasons for their popularity [2].

While there is a wide variety of e-cigarettes and vaping products, most of them share a common mechanism. A reservoir or cartridge filled with an e-cigarette liquid (or e-liquid) connected to a battery-powered heating metal coil, produces a mix of vapor and fine particles (aerosol), which is then inhaled through a mouthpiece [3]. Most e-liquids contain nicotine, often in high concentrations and flavoring agents. The solvents used for nicotine or flavored products are water based like propylene glycol. E-liquids may also be oil-based and contain substances like tetrahydrocannabinol (THC), the main psychoactive component found in cannabis [4]. They also contain small amounts of chemicals and heavy metals such as acrolein, acetaldehyde, nickel and lead, which can be toxic or carcinogenic **Table I** [2,5].

The use of e-cigarettes among youth is increasing in most parts of the world [6]. In the US, the prevalence of past-month e-cigarette use increased from 0.6% in 2011 to 10.5% in 2019 among middle school students (ages 11-14) and from 1.5% to 27.5% among high school students (ages 14-18) [7]. In Great Britain, lifetime e-cigarette use increased from 7% in 2016 to 11% in 2017 among 11-16 year-olds [8]. Estimates of lifetime e-cigarette use across Asia include 4.4% among 15-17 year-old adolescents in Taiwan [9], and 9.3% among secondary school students in Hong Kong [10].

E-CIGARETTE AND VAPING PRODUCTS

E-cigarettes come in many different shapes and sizes. Earlier models often resembled traditional cigarettes and had a limited appeal for youth [11]. The first surge in popularity among teens occurred between 2013-2015 with the proliferation of pen-like and larger, complex devices made available in a wide range of youth-friendly flavours [12]. A second rapid increase in popularity was between 2017-2019 with the arrival of small, pod-based devices using pre-filled cartridges [13]. **Fig. 1** presents a schematic representation of various e-cigarette devices [14].

The amount of nicotine contained in most e-liquids varies between 15 and 50 mg/mL. E-cigarettes exposes adolescents to nicotine toxicity and potential nicotine overdose [15] as they can absorb high amounts of nicotine in a short time period [16,17]. For example, a typical 2mL e-cigarette pod at 5% concentration would contain 100 mg of nicotine which could be consumed in as

Table I Substances Found in E-cigarette Liquids and Aerosols

Substances identified	*Carcinogens*
Nicotine	*Class 1 Potent carcinogens*
Humectants/solvents (e.g. propylene glycol and glycerol)	Formaldehyde
Flavorings	Benzene4-(methylnitroso-amino)-1-(3-pyridyl)-1-
Carbonyl compounds (including aldehydes)	Butanone
Tobacco alkaloids	Cadmium
Tobacco-specific nitrosamines (TSNAs)	*Class 2a Probable carcinogens*
Free radicals and reactive oxygen species (ROS)	Acetaldehyde
Volatile organic compounds (VOCs) and phenolic compounds	1,2-Propanediol
Residual solvents	Isoprene
Polycyclic aromatic hydrocarbons (PAHs)	Benzo(a)pyrene
Phthalates	Benzo(b)fluoranthene
Metals	Benzo(k)fluoranthene
Caffeine	Indenol(1,2,3-cd) pyrene
Pharmaceutical compounds	Chromium
+Microorganisms	Lead
Substances present in combustible cigarettes but typically not identified in e-cigarette aerosols	*Class 2b Possible carcinogens* Acrolein
Carbon monoxide	Toluene M,p-xylene
Tar	Phenol
	Benzo(e)pyrene
	Benzo(g,h,i) perylene
	Chrysene
	Nickel (more in e cig.)

Adapted from reference 11.

little as one hour with uninterrupted use [17,18]. The lethal dose of nicotine has been said to be between 30 and 60 mg for adults, but may be much higher [19].

HEALTH RISKS

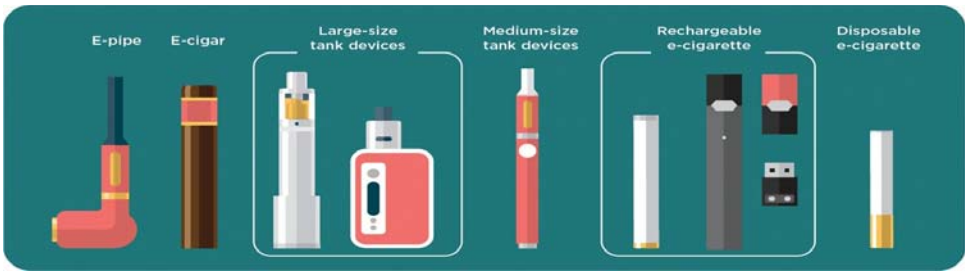
E-cigarettes are associated with several acute and long-term health risks. **Supp. Table I** summarizes the properties and physiological effects of the different constituents found in e-cigarette liquids [11].

Use of nicotine during adolescence is associated with altered brain development and long-term impairments in memory, attention capacity and executive functioning [20-23]. Consuming large amounts of nicotine through vaping can lead to nicotine toxicity, which presents with headaches, abdominal pain, nausea, vomiting, heart palpitations, hand tremors, difficulty concentrating, and in some cases, seizures and cardiac arrhythmia. Nicotine is also a long-term risk factor for poor cardiovascular health [24-26].

Regular nicotine use through vaping can also lead to withdrawal symptoms if adolescents try to quit or are temporarily unable to access vaping products. Withdrawal symptoms can appear after as little as a few weeks of use and can interfere with normal daily functioning [27-29].

Acute injuries like facial and limb burns due to malfunction of vaping devices have also been described [30]. Additionally, vaping aerosols include carcinogenic and irritating substances that may lead to chronic respiratory symptoms such as cough, bronchitis, asthma exacerbation and decreased exercise tolerance [31,32].

More than 2,800 cases of severe e-cigarette or vaping-associated lung injury (EVALI) were reported in Canada and the US in 2019 and early 2020, of which approximately 15% cases were reported in youth under the age of 18 years [33]. EVALI consists of a sterile inflammatory pneumonitis that presents with cough, chest pain, and shortness of breath, which can be severe and lead to hospitalization and even death [33]. While no cases have been reported in India, and much remains unknown about this condition, it is suspected that vitamin E acetate (found in several cannabis-containing e-liquids) may lead to such presentations [33].



Reproduced with permission from the Centers for Disease Control and Prevention, USA [14].

Fig. 1 E-cigarettes and other vaping devices.

CLINICAL MANAGEMENT OF E-CIGARETTE USE

Screening and Brief Intervention

Pediatricians should ask adolescent patients if they have tried vaping, if they currently vape, and discuss vaping-associated health risks with all adolescents. The discussion should include commercial brand names for more clarity and details should be asked about products and substances used, motives, context, frequency, intensity and motivations to quit if applicable [34,35]. Using standardized scales for nicotine dependence (such as the Hooked on Nicotine Checklist) or diagnostic criteria for cannabis use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) can also be useful to understand the severity of the vaping habit and addiction to nicotine and/or cannabis.

A 5-step Algorithm–The 5 A's

Ask, Advise, Assess, Assist, and Arrange–initially developed for smoking cessation, can also be a helpful framework for an effective vaping counseling intervention [35,36]. After asking about vaping, pediatricians should advise all adolescents not to initiate or to quit vaping and discuss one or two of the health risks associated with vaping (e.g. EVALI). Pediatricians can then assess the young person's motivation to quit or cut down, for instance, by using a 10-point scale (i.e. "on a scale from 1 to 10, how motivated are you to quit/cut down on vaping?"). Based on the response, the pediatrician can then offer to assist the adolescent with vaping cessation. Finally, pediatricians should arrange a follow-up plan, involving families and/or other health care providers when applicable.

Vaping Cessation

As there are no evidence-based pharmaceutical treatments tested specifically for adolescents with vaping addiction, the first line of treatment for vaping cessation relies on behavioral strategies. Strategies that have proven effective for tobacco dependence should be considered including individual or group counseling, motivational inter-viewing, cognitive-behavioral therapy, contingency management, mindfulness-based inter-ventions, as well as smartphone and web-based strategies [34,35].

Considering that most vaping liquids contain nicotine, often in high amounts, nicotine replacement therapy such as patches, gums and lozenge can be used safely with adolescents in addition to behavioral strategies [34]. The use of anti-craving medications such as bupropion and varenicline can also be considered alone or in addition to nicotine replacement [34].

E-cigarettes for Smoking Cessation: Adults vs Adolescents

A recent Cochrane review suggests that among adults, e-cigarettes used alone or in combination with other pharmaceuticals or behavioral methods may be of similar effectiveness for smoking cessation as approved nicotine replacement products [36]. People who oppose the recent ban on e-cigarettes in India, support that e-cigarettes are a valuable tool for Tobacco Harm Reduction (THR) as an aid for adult smokers hoping to quit smoking. A meta-analysis of 299 articles established that newer generations of e-cigarettes may serve as an efficient means of meeting the nicotine demand of a person addicted to smoking, with significantly reduced health consequences compared to conventional cigarettes [37].

However, whether this adult data can be extrapolated to youth remains unknown [36]. The evidence for pharmacotherapy for youth e-cigarette cessation remains extremely limited. Adolescents, with a still-developing pre-frontal cortex, are more vulnerable to the addictive properties of nicotine, which may impact the level to which adult data can be extrapolated.

Although, e-cigarette use may cause youth to transit to combustible tobacco products, it could also increase adult cessation of combustible tobacco cigarettes. The net public health effect, harm or benefit, of e-cigarettes depends on three factors: *i*) Effect on youth initiation of

combustible tobacco products, *ii*) Effect on adult cessation of combustible tobacco products, and *iii*) Intrinsic toxicity. E-cigarette use by adult smokers needs to lead to long-term abstinence from combustible tobacco cigarettes to lead to considerable benefit to public health. Without that, e-cigarette use could cause considerable harm due to the inherent harms of exposure to e-cigarette toxicants and to the harms related to potential subsequent combustible tobacco use by those who begin using e-cigarettes in their youth [11].

Prevention and Public Health Measures

In January 2020, the Society for Adolescent and Medicine issued a new policy statement by a collaborative group of Adolescent Medicine Providers from India, Canada, the US and the UK with recommendations to prevent e-cigarette use and protect youth from the harms of e-cigarettes (**Box I**) [38].

Box I Suggestions from the Society of Adolescent Health and Medicine to Prevent e-Cigarette Use

- Advocate for policies and regulations to prevent marketing and sales of e-cigarettes products to youth.
- Support public health–led education campaigns and educational curricula for schools, community programs, and health providers warning about the health risks of e-cigarette use by adolescents and young adults (AYAs).
- Increase research to develop evidence-based guidelines for e-cigarette prevention and cessation for AYAs.
- Support training for health providers to integrate screening for e-cigarette use into routine health visits for AYAs and increase the availability of evidence-based counseling and treatment resources for e-cigarette use cessation.

Reproduced with permission from Reference [38].

E-CIGARETTE USE IN INDIA

India has well-established tobacco cessation strategies, under the umbrella of the National Tobacco Control Programme (NTCP). The support for tobacco cessation is multipronged, ranging from brief advice to comprehensive counselling and support for nicotine-replacement therapy [39]. Tobacco consumption, mainly cigarette smoking, has declined by 1% between 2010 and 2017 in India, in response to several tobacco control measures [40]. There are recent surveys regarding tobacco consumption and e-cigarette sales and consumption in India [41]. A study on Indian Internet e-cigarette search query patterns concluded that searches for vaping products by Indians have been increasing over time [42].

Some of the most serious concerns have been expressed by school principals in Delhi regarding the increasing trend of youth vaping among young students [43]. The sale of vaping devices has spiraled upward since their introduction in the Indian market in 2007 to the point that many schools have become surrounded by vape shops [43]. In September 2019, India became one of the first countries to enact a complete ban on all e-cigarette products. This ban followed an intense period of discussion and debate weighing the advantages and potential disadvantages of such a ban [44], and the publication of a white paper from the Indian Council of Medical Research a few months prior [45].

CONCLUSION

Though the ban on e-cigarettes in India was mainly implemented to prevent e-cigarette use among youth, one must consider its potential negative effects among adults. There is still very limited data in India regarding use of e-cigarettes among adolescents, and even less so, regarding its effects on rates of youth use. Pediatricians can play a vital role in protecting youth against the known and potential risks of e-cigarette use. By staying informed on recent developments related to the health effects of e-cigarettes and offering effective screening and treatment interventions to youth who use them, Indian pediatricians can help mitigate the impacts of what has become a global risk for adolescents.

Acknowledgment: Dr. Samir Shah for help with referencing and table creation
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Chadi N, Hadland SE, Harris SK. Understanding the implications of the "vaping epidemic" among adolescents and young adults: A call for action. Subst Abuse. 2019;40:7-10.
2. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. 2016;1:5.
3. American Academy of Pediatrics: Section on Tobacco Control. Electronic Nicotine Delivery Systems. Pediatrics. 2015;136:1018-26.
4. Breitbarth AK, Morgan J, Jones AL. E-cigarettes – An unintended illicit drug delivery system. Drug Alcohol Depend. 2018;192:98-111.
5. Huang SJ, Xu YM, Lau ATY. Electronic cigarette: A recent update of its toxic effects on humans. J Cell Physiol. 2018; 233:4466-78.
6. Yoong SL, Stockings E, Chai LK, et al. Prevalence of electronic nicotine delivery systems (ENDS) use among youth globally: A systematic review and meta-analysis of country level data. Aust N Z J Public Health. 2018;42:303-8.
7. Cullen KA, Gentzke AS, Sawdey MD, et al. E-Cigarette use among youth in the United States. JAMA. 2019;322: 2095-103.
8. Bauld L, MacKintosh AM, Eastwood B, et al. Young people's use of e-cigarettes across the United Kingdom: Findings from five surveys 2015-2017. Int J Environ Res Public Health. 2017;14:973.

9. Chang HC, Tsai YW, Shiu MN, Wang YT, Chang PY. Elucidating challenges that electronic cigarettes pose to tobacco control in Asia: A population-based national survey in Taiwan. BMJ. 2017;7:e014263.
10. Chen J, Ho SY, Leung LT, Wang MP, Lam TH. School-level electronic cigarette use prevalence and student-level tobacco use intention and behaviours. Sci Rep. 2019;9:1690.
11. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board or Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic nicotinic-delivery systems. Public Health Consequences of E-Cigarettes. The National Academies Press; 2018:29894118.
12. Boak A, Elton-Marshall T, Mann RE, Hamilton HA. Drug use among Ontario students, 1977-2019: Detailed findings from the Ontario Student Drug Use and Health Survey (OSDUHS). Centre for Addiction and Mental Health. 2020
13. Singh S, Windle SB, Filion KB, et al. E-cigarettes and youth: Patterns of use, potential harms, and recommendations. Prev Med (Baltim). 2020;133:106009.
14. NIDA. Vaping Devices (2020, January 8). Vaping Devices (Electronic Cigarettes) Drug Facts. Accessed on June 24, 2020. Accessed from: *https://www.drugabuse.gov/publications/drugfacts/vaping-devices-electronic-cigarettes*
15. Chadi N, Moore-Hepburn C, Beno S, et al. Vaping-related injury and illness among Canadian children and adolescents: A one-time survey of pediatric providers. BMJ. Paediatrics Open. 2020;4:e000840.
16. Blank MD, Pearson J, Cobb CO, et al. What factors reliably predict electronic cigarette nicotine delivery? Tobacco Control. 2020;29:644-51.
17. Baassiri M, Talih S, Salman R, et al. Clouds and "throat hit": Effects of liquid composition on nicotine emissions and physical characteristics of electronic cigarette aerosols. Aerosol Sci Technol. 2017;51:1231-39.
18. EL-Hellani A, Salman R, El-Hage R, et al. Nicotine and carbonyl emissions from popular electronic cigarette products: Correlation to liquid composition and design characteristics. Nicotine Tob Res. 2018;20:215-23.
19. Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88:5-7.
20. Harvey J, Chadi N, Di Meglio G, et al. Strategies to promote smoking cessation among adolescents. Paediatr Child Heal. 2016;21:201-4.
21. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. JAMA Pediatr. 2017;171:788-97.
22. Goriounova NA, Mansvelder HD. Nicotine exposure during adolescence alters the rules for prefrontal cortical synaptic plasticity during adulthood. Front Synaptic Neurosci. 2012; 4:3.
23. Jankowski M, Krzystanek M, Zejda JE, et al. E-cigarettes are more addictive than traditional cigarettes—A study in highly educated young people. Int J Environ Res Public Health. 2019;16:2279.
24. Shao XM, Fang ZT. Severe acute toxicity of inhaled nicotine and e-Cigarettes: Seizures and cardiac arrhythmia. Chest. 2020;157:506-8.
25. Spindle TR, Talihab S, Hiler MM, et al. Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography. Drug Alcohol Depend. 2018;188:193-9.
26. Buchanan ND, Grimmer JA, Tanwar V, Schwieterman N, Mohler PJ, Wold LE. Cardiovascular risk of electronic cigarettes: A review of preclinical and clinical studies. Cardiovas Res. 2020;116:40-50.
27. Mclaughlin I, Dani JA, De Biasi M. Nicotine withdrawal. Curr Top Behav Neurosci. 2015;24:99-123.
28. Yingst JM, Foulds J, Veldheer S, et al. Nicotine absorption during electronic cigarette use among regular users. PLoS One. 2019;14:e0220300.
29. Yingst JM, Hrabovsky S, Hobkirk A, Trushin N, Richie JP, Foulds J. Nicotine absorption profile among regular users of a pod-based electronic nicotine delivery system. JAMA Netw Open. 2019;2:e1915494.
30. Hassan S, Anwar MU, Muthayya P, Jivan S. Burn injuries from exploding electronic cigarette batteries: An emerging public health hazard. J Plast Reconstr Aesthet Surg. 2016;69:1716-8.
31. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic cigarette use and respiratory symptoms in adolescents. Am J Respir Crit Care Med. 2017;195:1043-9.
32. Clapp PW, Jaspers I. Electronic cigarettes: Their constituents and potential links to asthma. Curr Allergy Asthma Rep. 2017;17:79.
33. Krishnasamy VP, Hallowell BD, Ko JY, et al. Update: Characteristics of a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury - United States, August 2019-January 2020. Morb Mortal Wkly Rep. 2020;69:90-4.
34. Hadland SE, Chadi N. Through the haze: What clinicians can do to address youth vaping. J Adolesc Heal. 2020;66:10-4.
35. Harvey J, Chadi N, and Canadian Paediatric Society, Adolescent Health Committee. Preventing smoking in children and adolescents: Recommendations for practice and policy. Paediatr Child Health. 2016;21:209-14.
36. Hartmann-Boyce J, Mc Robbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2020;10:CD010216.
37. Das S, Choudhary Y, Thangaminal V, Sharan RN. A systematic review and meta-analysis on the health and safety implications of electronic nicotine delivery systems. Indian J Clin Pract. 2019;29:1016-26..
38. The Society for Adolescent Health and Medicine. Protecting youth from the risks of electronic cigarettes. J Adoles Health. 2020;66:127-31.
39. Mohan P, Lando HA, Panneer S. Assessment of tobacco consumption and control in India. Indian J Clin Med. 2018;9:117991611875928.
40. World Health Organization. GATS 2: Global Adult tobacco survey, India 2016-17. Accessed on December 26, 2020. Available from: *https:// www.who.int/tobacco/surveillance/survey/gats/GATS_India_2016-17_FactSheet.pdf*
41. Sharan RN, Chanu TM, Chakrabarty TK, Farsalinos K. Patterns of tobacco and e-cigarette use status in India: A cross-sectional survey of 3000 vapers in eight Indian cities. Harm Reduct J. 2020;17:21.
42. Thavarajah R, Mohandoss AA, Ranganathan K, Kondalsamy-Chennakesavan S. Influence of legislations and news on Indian internet search query patterns of e-cigarettes. J Oral Maxillofac Pathol. 2017;21:194-202.
43. Chettri S. Vaping new headache for Delhi schools as fad catches on. Times of India. May 26, 2019. Available from: *https://timesofindia.indiatimes.com/city/delhi/delhi-vaping-new-headache-for-schools-as-fad-catches-on/articleshow/69501206.cms*
44. Kaur J, Rinkoo AV. A call for an urgent ban on e-cigarettes in India – A race against time. Global Hlth Promot. 2015; 22:71-4.
45. Chakma JK, Dhaliwal RS, Mehrotra R. White paper on electronic nicotine delivery system. Indian J Med Res. 2019;149:574-83.

Supplementary Table I Constituents Found in e-Cigarette Liquids and Aerosols and Their Physiological Effect on the Human Body

Constituent Properties	*Effects on Body*
Nicotine: A colorless, odorless liquid water-soluble alkaloid with an oily consistency, acquires a brown color and gives off a strong odor of tobacco when exposed to air.	• Short-acting stimulant with rewarding and addictive properties. • Triggers the release of epinephrine from the adrenal glands and sympathetic response (increase in heart rate, blood pressure, etc.) • Lethal dose in children and adolescents remains unknown.
HUMECTANTS/SOLVENTS *Propylene Glycol*: Clear, colorless, slightly syrupy liquid at room temperature. Practically odorless and tasteless, listed (GRAS) by the Food and Drug Administration (FDA).	• Allergic reactions, upper respiratory irritation, asthma. • Increased risk of toxicity in liver and kidney impairment and high-dose oral or intravenous administration. • No data for vapor inhalation & absorption.
Glycerol (Glycerine): Oily, hygroscopic liquid with a warm, sweet taste. Less irritant than PG Listed GRAS by FDA	Mild headache, dizziness, nausea, vomiting, thirst and diarrhea at unspecified dosages
Ethylene Glycol: An odorless, clear, slightly viscous liquid. Where present, it is at levels that are not likely to contribute significantly to adverse health effects.	• It is a respiratory irritant and is associated with markedly enhanced toxicological hazards when compared with conventionally used glycerol and PG
Flavorings: More than 7,000 unique e-liquid flavors available. Concentrations vary widely. Fruity e-cigarette are often preferred among both smokers and non-smokers. Diacetyl, acetylpropionyl (2,3-pentanedione), acetoin, Cinnamaldehyde are chemicals used. Often named as a primary reason for e-cigarette use.	• Flavors may have cooling and local anesthetic effects • Reasons for uses include increased satisfaction and enjoyment, variety and customization, better feel and taste than cigarettes, food craving suppression, social impacts. • Menthol reinforces effects of nicotine on tobacco smoking behaviors - results in increased nicotine dependence and a greater chance of tobacco-attributable disease. • Formation of aldehydes—vanillin and ethyl vanillin, thujone, menthol (pulegone, eucalyptol) which is associated with adverse respiratory health outcomes. Increased incidences of chronic cough, bronchitis, asthma, and bronchiolitis obliterans. • Even at low concentrations, cinnamaldehyde in e-cigarette products is cytotoxic, genotoxic, adversely affects cell

Constituent Properties	*Effects on Body*
	processes and survival. It may also impair homeostasis in the respiratory system.
Carbonyl compounds: Formaldehyde, Acetaldehyde, Acrolein, Glyoxal, Propanal, Crotonaldehyde, Butanal and Methylglyoxal which have been found in e-cigarette aerosols. Aerosols generated from PG-based e-liquids were found to have the highest levels of carbonyls. Compared to combustible cigarettes, very high levels of formaldehyde are found in aerosols from E-cig	• Lower liquid levels within the cartridges or tanks may increase air flow and promote overheating of the wire if no safety features are incorporated to maintain a constant and lower temperature. This leads to the formation of carbonyls, which are potentially hazardous and/or carcinogenic
Minor Tobacco Alkaloids: Impurities including minor alkaloids: Nornicotine, Anatabine, Anabasine, Cotinine, Nicotine *N*-Oxides, Myosmine, Nicotyrine and Nornicotyrine. These minor alkaloids may arise from biosynthetic processes in the living tobacco plant or by bacterial action or oxidation during tobacco processing and can thus be found in e-cigarette liquids derived from tobacco products	Nicotine-related impurities are thought to be less toxic than nicotine
Tobacco-specific nitrosamines: *N*'-nitrosoanatabine (NNN), NNK, *N*'-nitrosoanabasine (NAB). TSNAs are potent carcinogenic chemicals.	Carcinogenic potential
Free Radicals and Reactive Oxygen Species (Ros): Activating the e-cigarette's heating element and aerosolizing the e-liquid produces ROS; these species are drawn into the lungs directly from the device. Oxidants are also derived from a device's lithiumion battery, similar to that used in combustible tobacco cigarette filters and e-cigarette cartomizers	They cause oxidative stress, which damages cellular proliferation, metabolism, and health, and can be involved in the development of several cardiovascular, respiratory neurodegenerative disorders, rheumatoid arthritis, and some types of cancers.
Volatile Organic Compounds (Vocs) And Phenols: Benzene, Toluene, Ethylbenzene, *M*-Xylene, *P*-Xylene, *O*-Xylene, Styrene, Ethyl Acetate, Ethanol, Methanol, Pyridine, Acetylpyrazine, 2,3,5-Trimethylpyrazine and Octa- Methylcyclotetrasiloxane	• Irritant to upper and lower respiratory tract • Central nervous system and end-organ damage at high concentrations • Carcinogenic potential
Residual Solvents: The thermal degradation of sugars can produce toxic furans, such as 5-hydroxymethylfurfural and furfural	• Irritant to Upper Respiratory Tract
Polycyclic aromatic hydrocarbons (PAHs): Products of combustion which can form small particles or bind to other small particles	• Irritant to Upper Respiratory Tract • Carcinogenic potential

Constituent Properties	*Effects on Body*
Phthalates: Diethyl phthalate (DEP) and diethylhexyl phthalate (DEHP) IARC classifies DEHP as "possibly carcinogenic to humans".	• These antiandrogenic, estrogen-like compounds have been shown to lead to gynecomastia
Metals: Chromium, Nickel, Lead, Manganese, Aluminum, Tin, and Iron in e-liquid emissions originate from several parts of the device, including the metallic coil, a complex alloy that heats the e-liquid to produce the aerosol that is inhaled by the user. Lead, Nickel, Tin quantified at significantly higher concentrations in e-cigarette aerosols than combustible tobacco smoke	• Specific Metal related toxicities
Caffeine: E-liquid flavors like coffee, tea, chocolate, and energy drinks.	• Very little is known about the effects of caffeine inhalation, and health risks cannot be estimated.
Pharmaceutical drugs: Weight loss medication (Rimonabant) not approved by FDA (2007) has been found in e-liquids. E-liquids can contain an analogue (amino tadalafil) active ingredient found in Cialis, an erectile dysfunction drug	• Adverse neurological events such as seizures and suicide • Undetermined or harmful health effects
Microorganisms: Bacteria, fungi, parasites	• Presence of micro-organisms could lead to bacterial/fungal/parasitic infections

Adapted from: Eaton DL, Kwan LY, Stratton K, editors. Public Health Consequences of E-Cigarettes-Toxicology of E-Cigarette Constituents. National Academies Press (US). 2018; 5

RESEARCH PAPER

Two-hourly vs Three-hourly Feeding in Very Low Birthweight Neonates: *A Randomized Controlled Trial*

ANITA YADAV, NAUSHEEN SIDDIQUI AND PRADEEP KUMAR DEBATA

From Neonatal Division, Department of Pediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India. Correspondence to: Dr Pradeep Kumar Debata. B-21, G-1, B-Block, Dilshad Garden, Delhi 110 095, India. drpkdebata@gmail.com
Received: October 28, 2019; Initial review: January 02, 2020; Accepted: October 1, 2020.

Background*:* There is no consensus regarding the feeding interval in very low birth weight (VLBW) babies. If 2-hourly feeding schedule is feasible without increasing harm to the neonate, the nursing time consumed in the feeding of VLBW babies can be reduced.

Objective*:* To study whether 3-hourly feeding is non-inferior to 2-hourly feeding with respect to time to reach full feeds in VLBW neonates.

Design*:* Open-label, randomized controlled trial.

Subjects: 350 Neonates weighing between 1000 to 1500 grams, in whom feed could be started within 96 hours of life randomized to either 2-hourly or 3-hourly feeding schedule.

Primary outcome: Time to achieve full enteral feed.

Results*:* The primary outcome of time to achieve full enteral feed was comparable in the two feeding schedule groups (median 5 days IQR 4-6 days in both groups; *P*=0.665). Among the secondary outcomes, there were no significant differences in incidence of hypoglycemia (RR 0.86; 95% CI: 0.29-2.5) feed intolerance (RR 1.08: 95%CI: 0.5-2.3), and necrotizing enterocolitis (RR 0.8; 95% CI: 0.22-2.3) in both the groups.

Conclusion*:* Three hourly feeding does not increase the risk of hypoglycemia, *necrotizing enterocolitis* or feed intolerance.

Keywords: *Enteral feeding, Feeding Interval, Feed intolerance, Hypoglycemia, Infant feeding, Necrotizing enterocolitis.*

Trial Registration: CTRI/2018/01/016630

Published online: January 01, 2021; ***PII*:** S097475591600274

Feeding of very low birthweight (VLBW) infants (1000-1500 g) is relatively difficult because majority of them are born with inadequate feeding skills, have feed intolerance, and are at an increased risk of necrotizing enterocolitis (NEC). Early initiation of enteral feeding is preferred for preterm VLBW babies with mothers own milk for less NEC and better neurodevelopment outcomes and preventing gastric atrophy and improving gut motility and reaching full feeds early [3-6]. Bolus feeding is preferred for natural surge of gut hormones and helps in reaching full enteral feed early as compared to continuous feeding [7-9].

Regarding, the different feeding intervals, on one hand, less frequent feeding (3-hourly) decreases nursing workload, reduces infant handling and chances of acquiring infections [10]. On the other, it also leads to higher volume per feed, which may decrease feed tolerance. Feeding two-hourly feeds delivers a smaller volume per feed, which is more easily tolerated by the preterm and causes less gastric distension and less gastro-esophageal reflux [11]. There is no consensus regarding the feeding interval in VLBW babies. Feeding in NICUs requires a major part of the nursing time. The actual workload of nurses in the NICU is tremendous and nurse-to-patient ratio is often inadequate in low- and middle-income countries (LMICs) [12,13]. Therefore, we conducted the study to determine whether a three-hourly feeding schedule is non-inferior to a two-hourly feeding schedule with regards to time to achieve full enteral feeds in VLBW neonates.

METHODS

This open-label randomized controlled trial was conducted from January, 2018 to March, 2019 in a level III neonatal care unit. Institutional ethics committee approved the study protocol. All inborn neonates weighing between 1000 g and 1500 g, in whom feed could be started within 96 hours of life, were included in the study. The exclusion criteria were major congenital malformations including tracheoesophageal fistula, esophageal atresia and duodenal atresia that interfered or delayed the feed initiation; severe perinatal asphyxia (APGAR score of <5 at 5 min) or encephalopathy due to any reason; infants with absent or reversed end diastolic flow (AEDF/REDF) in antenatal USG; and infants who were severely sick, on invasive ventilation or in shock. Small for gestational age (SGA) was defined as birth-weight less than 10th percentile for that gestation as per the Intergrowth charts [14].

The primary outcome was to compare the time to achieve full enteral feed between the two groups of VLBW infants receiving 2-hourly and 3-hourly feed. The secondary objectives were to compare the incidence of hypoglycemia, feed intolerance and NEC stage 2 or 3 between the two groups. A subgroup analysis of the same outcomes between babies weighing 1000-1250 g and 1250-1500 g was decided a priori.

Full enteral feed was defined as 150 mL/kg/day of enteral feeds, and hypoglycemia was defined as blood glucose concentration <45mg/dL [15]. Feed intolerance was defined as abdominal distension (abdominal girth ≥2 cm), with blood or bile stained aspirates or vomiting or pre-feed gastric residual volume more than 50% of feed volume; the latter checked only once feeds reached 5 mL/kg volume [16]. NEC was defined as per the modified Bells staging.

Parents of the VLBW babies delivered in the hospital labor room were approached for informed written consent for participation in the study. Those infants who satisfied the eligibility criteria were stratified as per the weight (1000-1250 g and 1251-1500 g, and were randomly allocated to one of the intervention groups using a web based allocation sequence generator. A person not involved in the study generated the randomization. Randomization was done with blocks of variable sizes and the allocations were concealed, by keeping the allocation sequence in serially numbered sealed and opaque envelopes. The nature of intervention prevented blinding of the intervention from the investi-gators and the treating team. However, the statistician was blinded from the allocation details.

The standard group received enteral feed every 2 hours and the experimental group at 3-hourly intervals. Feeding was started as expressed breast milk as soon as the infant was stable. Preterm formula was used if breast milk was insufficient. The feeding protocol of the unit was uniformly followed for both groups. Feeding was initiated and increased by 30 mL/kg/day in babies weighing 1000-1250 g and as complete total enteral feeds (as per the daily standard fluid requirement) in the 1251 to 1500 g weight group babies. In the former group, intravenous fluid was given till enteral feed reached a volume of 120 mL/kg/day. Babies were fed through orogastric tube using the gravity method or with the help of cup/*paladi*, as per gestational maturity. In neonates on oral feeding, the abdominal girth was measured every 12 hours. If the abdominal girth increased by ≥2 cm or if baby vomited, gastric residual was checked. Once feed volume was more than 5 mL/kg; if aspirate was milky and <25% of feed volume, feeds were continued and if the aspirate was 25-50%, next feed volume was reduced equal to the aspirate volume. One or two feeds were withheld if the aspirate volume was >50% of the feed volume or 5 mL/kg (whichever is higher), and feeds were restarted with abdominal girth monitoring. If the feed intolerance recurred associated with systemic signs and symptoms or if the aspirate was bile or blood-stained, feeds were withheld for at least 24 hours and restarted when the issue resolved. Dextrose monitoring was done using Gluco-care sense glucometer at 1-hour, 3-hours, 6-hours and then 12-hourly till 72 hours of life or if baby was symptomatic. All blood sugar estimates in the hypoglycemia range were confirmed using laboratory sample. All the hypoglycemia episodes were treated as per the standard protocol of the unit.

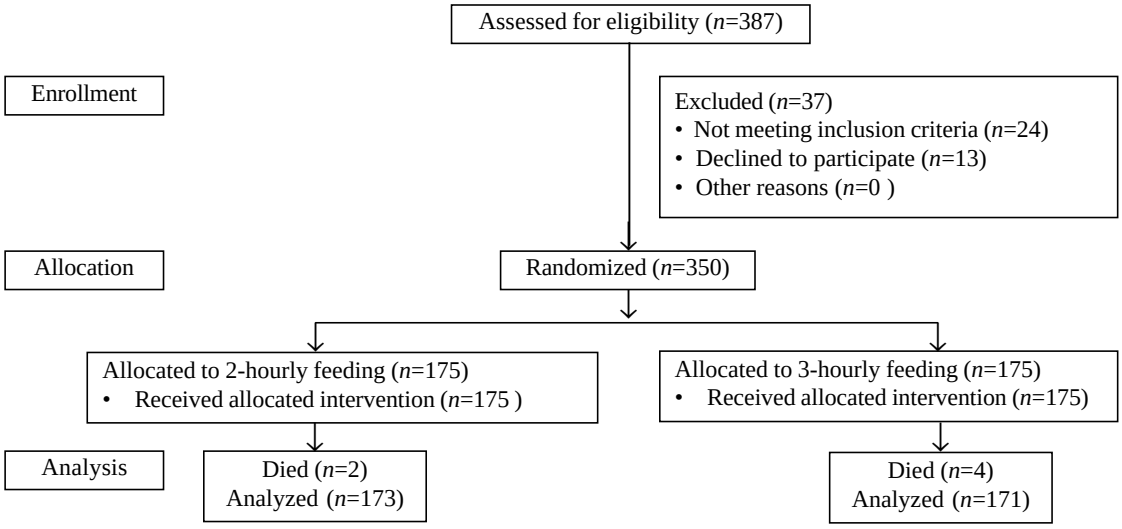


Fig. 1 Study flow chart.

The infants were weighed daily by the nurse using a standardized and well calibrated digital weighing machine (±5g) (Seca). A neonate was considered to have completed the study once the infant reached full enteral feeds (≥150 mL/kg/day) and maintained it for 48 hours without any feed intolerance [17].

Taking the mean time difference to achieve full enteral feed as 1.1 days [18], the minimum required sample size, with 90% power of study and 5% level of significance was 350 (175 patients per group).

Statistical analyses: Categorical outcome variables were analyzed by Chi-square test with continuity correction or Fisher exact test. Estimates of strength of association were deduced by calculating relative risks with their respective 95% confidence intervals. An intention-to-treat analysis was done. $P<0.05$ was considered significant.

RESULTS

The flow of subjects in the study is shown in **Fig. 1**. The baseline demographic and clinical characteristics were comparable between the two groups (**Table I**). Six babies died (2 in 2-hourly and 4 in 3-hourly group). Time to achieve full enteral feed was comparable in the two groups of neonates [median (IQR), 5 days (4-6) in both groups; $P=0.665$]. We performed sensitivity analysis using worst case scenario, assigning maximum (15) days to reach full feeds by dead babies in 3-hourly group and minimum (2) days to 2-hourly group. The hazard ratio (95% CI) was 1.022 (0.829-1.262) with $P= 0.88$ (**Fig. 2**).

Range of time for attaining full enteral feeds was 3-15 days. Eleven neonates were outliers and reached full enteral feeds between 10-15 days of life. None of these outliers had hypoglycemia. One baby was of 29 weeks gestation and had no other morbidities. Rest of the babies were of 32-34 weeks gestation, all 10 had feed intolerance,

Table I Baseline Characteristics of the Very Low Birthweight Neonates in the Study

	2-hourly feeding (n=175)	*3-hourly feeding (n=175)*
Preterm	169 (96.6)	171 (97.1)
Gestation (wk)[a]	32.3 (2.3)	32.5 (2.3)
Male	104 (59.4)	104 (59.4)
Appropriate for gestational age	110 (62.9)	101 (57.7)
Birthweight 1000-1250 g	62 (35.4)	64 (36.6)
Birthweight 1251-1500 g	113 (64.6)	111 (63.4)
Birthweight (kg)[a]	1.32 (0.14)	1.31 (0.15)

Values in no. (%) except [a]mean (SD).

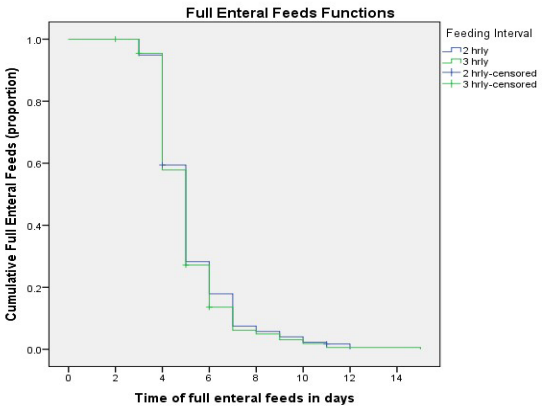


Fig. 2 Kaplan Meier graph for time to reaching full enteral feed volume by infants in the 2-hourly and 3-hourly feeding groups.

9 had NEC and one had ileal atresia. Among the secondary outcomes, there were no significant differences in incidence of hypoglycaemia, feed intolerance and NEC in both the groups (**Table II**). Hypoglycemia, feed intolerance and NEC occurred at mean (SD) 38.8 (34.31) and 49.43 (31.53) hours of life, 29.8 (30.47) and 28.8 (28.11) hours of life and 5.8 (3.7) and 7.7 (0.96) days of life in the two-hourly and three-hourly feeding groups, respectively.

DISCUSSION

In this open-label, randomized controlled trial, there was no significant difference in the time taken to achieve full enteral feeds between very low birthweight infant receiving 2-hourly or 3-hourly feeds.

Two babies were given two feeds at two-hourly intervals rather than three-hourly. One baby, found to have ileal atresia after enrolment, reached full feeds on day 15 of life. An important risk of bias though was the lack of blinding, which was impossible because of the nature of the interventions. The standardized feeding protocol and the use of pre-defined outcome measures may have reduced the risk of this bias. In this study, the

Table II Secondary Outcome Measures in Neonates in the Two-hourly vs Three-hourly Feeding Groups

Outcome	*Feeding schedule*		*RR (95% CI)*
	2-hourly (n=175)	*3-hourly (n=175)*	
Hypoglycemia	6 (3.4)	7(4.0)	0.86 (0.29-2.49)
Feed intolerance	13 (7.4)	12 (6.9)	1.08 (0.5-2.3)
NEC	4 (2.3)	5 (2.9)	0.8 (0.22-2.29)

Values in no. (%); NEC: Necrotizing enterocolitis.

Appropriate for gestational age

WHAT IS ALREADY KNOWN?

- Intermittent two-hourly bolus feeding is recommended for very low birthweight neonates.

WHAT THIS STUDY ADDS?

- It is safe to administer three-hourly feeding schedule for very low birthweight babies weighing 1000-1500 gram.

advancement of enteral feeds was fast (at the rate of 30 mL/kg/day) which is the current norm to achieve early FEF [20]. Formula was used in 14.9% babies and there was no difference in its use in both the groups. The study was adequately powered to detect the difference of 1 day in the duration to achieve full feeding, which was the primary outcome.Time to reach full enteral feeds was kept as a primary outcome as it was a very important outcome for neonate. Once intravenous cannula and fluids are removed, the exposure of baby to risk of sepsis goes down indirectly [17]. NEC and mortality though are hard outcomes but rare, and sample size would have gone very high because of lower event rate.There were three protocol deviations.

However, our results are similar to previous studies [18,20], even though, Ibrahim, et al. [18] had a slower advancement of feeding.The total nursing time spent on feeding per day has also been shown to be significantly less in three-hourly groups [20,21].

DeMauro, et al. [22] did a retrospective cohort study in infants weighing 500-1500 grams and found that achieving full enteral feed was better in neonates receiving 2-hourly feeds. However, this was a retrospective study with a different population, and they used continuous feeding in cases of severe feed intolerance and excluded these from further analyses [22]. Others [23,24] have also reported similar results.

Though this study showed that there was no difference in time to reach full feeds and incidence of adverse events like feed intolerance, NEC and hypoglycemia, a non-inferiority trial can be planned to show that three-hourly feeding is noninferior to two-hourly feeding.

Razak [25] carried out systematic review and meta-analysis in 2019, including seven RCTs and three observational studies comprising 952 babies and found no significant differences in the outcomes: time to reach full enteral feeding, necrotizing enterocolitis, feed intolerance, and hypoglycemia. Dutta, et al. [17] systematically reviewed the literature and gave suggestion to administer three-hourly feed for babies weighing >1250 g and found insufficient evidence to choose between two-hourly versus three-hourly feed for babies weighing ≤1250 g. Further subgroup analysis of our study will give more information about the neonates in two different weight groups of 1000 to 1250 and 1251 to 1500 grams.

Three-hourly feeding in very low birthweight babies does not increase the time to achieve full enteral feeds or increase the incidence of feed intolerance, hypoglycemia and NEC.

Ethics clearance: Institutional ethics committee, Vardhman Mahavir Medical College, Delhi: No. IEC/VMMC/SJH/Thesis/October/2017-162 dated October 30, 2017.
Contributors: AY: supervised the investigation and made the initial manuscript; NS: investigation and collected the data; PD: conceptualized the research, made the protocol and supervised the study and made the final manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Saifon C, Joshua PV, Ann-Beth M, et al. Global, regional, and national estimates of levels of preterm birth in 2014: A systematic review and modelling analysis. Lancet Global Health. 2019;7:e37-46.
2. UN Inter-Agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality: Report 2017. New York: United Nations Children's Fund, 2017.
3. Morgan J, Young L, Mc Guire W. Delayed introduction of progressive enteral feeds to prevent NEC in very low birthweight infants. Cochrane Database Syst Rev. 2014;12: CD001970.
4. Nangia S, Vadivel V, Thukral A, Saili A. Early total enteral feeding versus conventional enteral feeding in stable very low birthweight infants: A randomised control trial. Neonatology. 2019;115:256-62.
5. Gibertoni T, Corvaglia L, Vandini S, et al. Positive effect of human milk feeding during NICU hospitalization on 24-month neurodevelopment of VLBW infant: An Italian Cohort Study. PLoS One. 2015;10: e0116552:1-13.
6. McClure R.J. Trophic feeding of the preterm infant. Acta Paediatr. 2001;90:19-21.
7. Rayyan M, Rommel N, Allegaert K. The fate of fat: Pre-exposure fat losses during nasogastric tube feeding in preterm newborns. Nutrients. 2015;7:6213-23.
8. Rogers SP, Hicks PD, Hamzo M, Veit LE, Abrams SA.

Continuous feedings of fortified human milk lead to nutrient losses of fat, calcium and phosphorous. Nutrients. 2010;2:230-40.
9. Premji S, Chessel L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. Cochrane Database Syst Rev. 2002; 4:CD001819.
10. Jeannette AR, Douglas S, Thelma P, Jeffrey H, Michael K, Eileen TL. Nurses staffing and NICU infection rates. AMA Pediatr. 2013;167:444-50.
11. Lane AJ, Coombs RC, Evans DH, Levin RJ. Effect of feed interval and feed type on splanchnic haemodynamic. Arch Dis Child Fetal Neonatal Ed. 1998;79:F49-53.
12. Sherenian M, Profit J, Schmidt B, *et al.* Nurse-to patient ratios and neonatal outcomes: A brief systematic review. Neonatology. 2013; 104:179-83.
13. Neogi SB, Malhotra S, Zodpey S, Mohan P. Assessment of special care newborn units in India. J Health Popul Nutr. 2011;29:500-9.
14. Villar J. Ismail L.C, Victoria CG. International standards for newborn weight, length, head circumference by gestational age and sex: The newborn cross-sectional study of the INTERGROWTH-21st project. Lancet. 2014;384:857-68.
15. Adamkin DH. Neonatal hypoglycemia. Semin Fetal Neonatal Med. 2017;22:36-41.
16. Härtel C, Haase B, Browning-Carmo K, et al. Does the enteral feeding advancement affect short-term outcomes in very low birthweight infants? J. Pediatr Gastroenterol Nutr. 2009;48:464-70.
17. Dutta S, Singh B, Chessell L, et al. Guidelines for feeding very low birthweight infants. Nutrients. 2015;7:423-42.
18. Ibrahim NR, Van Rostenberghe H, Ho JJ. Short versus long feeding interval for bolus feedings in very preterm infants. Cochrane Database Sys Rev. 2016; CD012322.
19. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birthweight infants. Cochrane Database Sys Rev. 2015:CD001241.
20. Dhingra A, Agrawal SK, Kumar P, Narang A. A randomised controlled trail of two feeding schedules in neonates weighing less than or equal to 1750g. J Matern Fetal Neonatal Med. 2009;22:198-203.
21. McCallie KR, Lee HC, Mayer O, Cohen RS, Hintz SR, Rhine WD. Improved outcomes with a standardized feeding protocol for very low birthweight infants. J Perinatol. 2011;31:S61-7.
22. DeMauro SB, Abbasi S, Lorch S. The impact of feeding interval on feeding outcomes in VLBW infants. J Perinatol. 2011;31:481-6.
23. Rudiger M, Herrmann S, Schmalisch G, Wauer RR, Hammer H, Tschirch E. Comparison of 2-hourly versus 3-hourly enteral feeding in extremely low birthweight infants, commencing after birth. Acta Paediatr. 2008;97:764-9.
24. Chu E, Freck S, Zhang L, Bhakta KY, Mikhael M. Three-hourly feeding intervals are associated with faster advancement in very preterm infants. Early Hum Dev. 2019;131:1-5.
25. Razak A. Two-hourly versus three-hourly feeding in very low-birth-weight infants: A systematic review and meta-analysis. Am J Perinatol. 2020;37:898-906.

RESEARCH PAPER

Catch-up and Catch-down Growth in Term Healthy Indian Infants From Birth to Two Years: *A Prospective Cohort Study*

VANDANA JAIN, BRIJESH KUMAR AND SAPNA KHATAK

From Pediatric Endocrinology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India. Correspondence to: Dr Vandana Jain, Professor, Pediatric Endocrinology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India. vandanajain2005@hotmail.com

Received: September 20, 2019; Initial review: December 30, 2019; Accepted: October 1, 2020

Background: Catch-up in the first two years of life may help in reducing the growth deficit.

Objective: To study growth pattern of term infants from birth to 2 years, focusing on catch-up and catch-down growth (increase or decrease in *z*-score >0.67) in weight and length.

Study design: Prospective birth cohort.

Participants: 262 healthy term infants with birthweight 1800-4000 g.

Intervention: Serial assessment of anthropometric parameters at birth, 3.5 month, 1 year and 2 year of age.

Outcomes: Proportion, timing and determinants of catch-up and catch-down growth.

Results: Weight catch-up between birth to 3.5 mo, 1 y, and 2 y was seen in 18%, 41% and 38%; and weight catch-down in 27%, 25% and 23%, respectively. Between birth and 2 y, change in weight *z*-score was inversely related to birthweight (β -3.754, *P*<0.001) and directly to caloric intake at 2 y (β 0.003, *P*<0.001). Mean (SD) birthweights of infants with catch-up, steady growth and catch-down were 2.6 (0.4), 2.9 (0.4) and 3.1 (0.4) kg, respectively (*P*<0.001). Catch-up and catch-down in length between birth and 2 y were present in 30% and 33% of the infants, respectively. Length *z*-scores at 2 y but not at birth were positively correlated with mothers' (r=0.21, *P*=0.002) and fathers' height (r=0.22, *P*=0.001).

Conclusion: Nearly two-thirds of healthy term infants experienced either catch-up or catch-down in weight and length first 2 years of life. Infants' birthweight and length at birth, caloric intake, and parents' heights are important determinants of their growth patterns.

Keywords: *Adiposity, Growth trajectory, Low birthweight, Stunting, Undernutrition*.

Published online: January 02, 2021; ***PII*:** S097475591600273

The average birthweight of Indian newborns is lower in comparison to that of newborns in other countries. The mean (SD) birthweight of Indian babies from affluent families without any obvious constraints was 2.9 (0.4) kg as compared to 3.3 (0.5) for the pooled data from other eight sites in Intergrowth-21st study [1]. A similar trend was present for birth length [1]. Whether these differences were due to prenatal growth constraint or related to ethnic and other physiological variations, and whether Indian newborns recover from the growth deficit is not clearly understood.

The upward crossing of centiles seen in babies with low birthweight is often described as catch-up growth. During growth monitoring in infancy, it implies that the size at birth was smaller than the infant's potential to grow as a consequence of constraints during fetal period. However, it is simplistic to assume that catch-up growth occurs only in small for gestational age (SGA) infants. In a proportion of infants, postnatal growth acceleration may not reflect catch-up growth from constraints, but excessive weight gain as a result of overfeeding or other genetic/environmental factors. Thus, catch-up growth may not always be desirable and instead pose a greater risk of future obesity, metabolic syndrome and type 2 diabetes [2-7]. The reverse phenomena, i.e., downward crossing of centiles of weight or length are generally attributed to growth faltering or under-nutrition [8]. However, this may reflect a true catch-down in infants with excess antenatal growth for their genetic potential who revert to their physiological growth curve [9,10].

The present study assessed the growth pattern of term healthy infants from birth to two years of age, and evaluated timing and determinants of catch-up growth and catch-down growth in weight and length.

METHODS

This prospective cohort study was conducted at All India Institute of Medical Sciences, New Delhi during 2013-2016 after approval from the ethics committee. Healthy term singleton infants were enrolled at birth after informed consent from the parents. Infants with birthweight <1800 gram and >4000 gram, any illness requiring neonatal intensive care unit stay or intravenous fluid therapy for >48 hours, maternal inability or contraindication to

breastfeeding, families belonging to lower socio-economic strata, and large family size (more than three alive siblings) were excluded.

Gestational age was calculated based on last menstrual period. Infants were classified into small, appropriate and large for gestational age (SGA, AGA and LGA, respectively) using Indian intrauterine growth curves [11]. Socioeconomic status was determined based on the income, education and occupation of head of the household [12]. Maternal serial weights were noted from her antenatal records, and weight of father was measured with a bathroom scale. Height of both parents was measured using stadiometer to an accuracy of 0.5 cm.

Nude weight of infant was measured at birth by electronic weighing balance with a sensitivity of 10 gram (Seca 354, Seca GmbH). Length and skinfold thicknesses at biceps, triceps, subscapular and supra-iliac sites were measured within 48 hours of birth using infant measuring board (Seca 417, Seca GmbH), and Holtain calipers (Holtain Ltd), respectively. All measurements were made in duplicate and averaged. Anthropometric equipment were calibrated regularly. Percentage body fat (BF%) was calculated from the sum of skinfolds using the equations given by Weststrate and Deurenberg [13]. Weight and length were converted to *z*-scores using World Health Organization (WHO) Anthro plus software. Anthropometric measurements (weight, length and skinfold thicknesses) were repeated at 3.5 months (±2 weeks), 1 year (±1 month), and 2 years (±2 month) of age. Standing height was measured for all children at 2 years. If the age of the child was less than completed 24 months, 0.7 cm was added to the standing height before calculation of *z*-score to make it equivalent to supine length. Feeding of infants was assessed using infant and young child feeding (IYCF) questionnaire [14], and detailed dietary intake was recorded at 1 year and 2 year visits using a one-month semi-quantitative food frequency questionnaire. Caloric intake was calculated by a qualified dietician.

Catch-up growth and catch-down growth were defined as an increase or decrease in *z*-score of > 0.67 between two time points [4]. This approximately represents the width of each major percentile band on standard growth charts (e.g., 10th to 25th or 25th to 50th), and therefore can be considered clinically significant.

Sample size was estimated as 225 taking prevalence of weight catch-up between birth and 2 years as 30% [4], with precision of 6%. Considering the possibility of upto 15% attrition of the cohort, 262 infants were enrolled.

Statistical analyses: The proportion of infants who experienced catch-up growth and catch-down growth during the different time periods was calculated. The anthropometric measurements, adiposity and caloric intake were compared between infants with and without catch-up growth. Factors that could affect the increment in weight for age *z*-score between birth to 3.5 months, birth to 1 year and birth to 2 year, including parents' height and BMI, maternal parity, socio-economic status, and infants' birthweight, gender and feeding were evaluated by linear regression. $P < 0.05$ was considered as significant.

RESULTS

A total of 262 newborns (150 boys) were enrolled. The baseline characteristics of the cohort are shown in **Table I** and study flow chart is presented in **Fig. 1**. **Table II** summarizes the anthropometric parameters as absolute

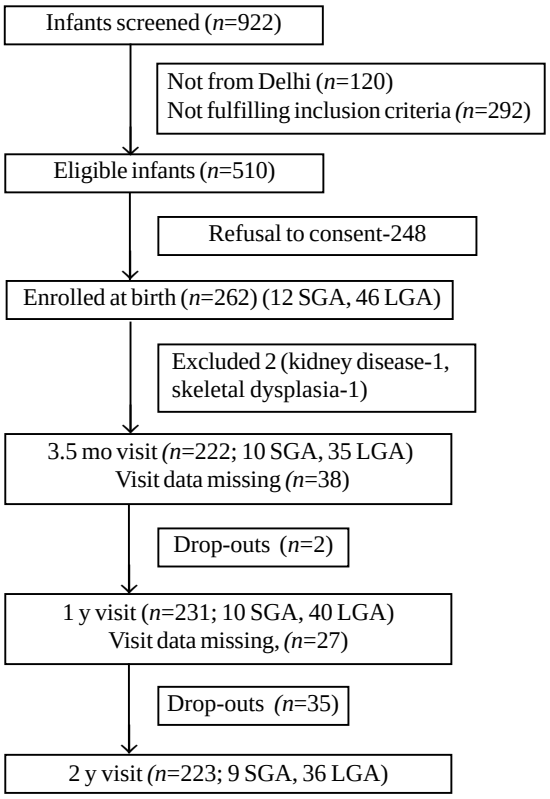
Table I Baseline Characteristics of Newborns and Parents (*N*=262)

Parameters	*Mean (SD)*
Birthweight, g	2863 (418)
Birthweight categories, n (%)	
<2500 g	55 (21)
2500-3000 g	117 (45)
>3000 g	90 (34)
Small for gestational age	12 (4.6)
Large for gestational age	46 (17.6)
Gestational age, wk	38.3 (1.0)
Birth length, cm	48.4 (2.2)
Maternal age, y	27.3 (4.6)
Maternal preconception weight, kg	55.0 (9.3)
Maternal height, cm	154 (4)
Maternal preconception BMI, kg/m^2	23.6 (4.0)
Maternal BMI categories, n (%)	
BMI <18.5 kg/m^2, *n (%)*	21 (8.5)
BMI <25 kg/m^2, *n (%)*	79 (31.5)
Paternal height, cm	168 (7)
Paternal BMI, kg/m^2	24.9 (3.6)
Socioeconomic status, n (%)	
Upper	22 (8)
Upper middle	82 (32)
Lower middle	158 (60)
Maternal education, n (%)	
Graduate and above	136 (52)
Matriculation	87 (33)
Less than matriculation	38 (15)

Values in mean (SD) or as stated. BMI: Body mass index.

values, z-scores, and proportion of infants with z-scores < -2 at birth and follow-up. At 2 years, 11 (4.9%) children had BMI z-score > +2, of whom 4 were born LGA while the rest were born AGA.

The weight gain trajectories of the infants with catch-up growth; catch-down growth or steady growth on follow-up were analyzed (**Table III**). While in the first year of life, 41% of babies showed catch-up growth and 25% showed catch-down growth, the reverse pattern was noted in the second year, with a higher proportion showing catch-down (38%) compared to catch-up (29%). The cohort was divided into three tertiles based on WAZ at birth (WAZ_0). For infants in the lowest WAZ_0 tertile, the median (IQR) WAZ increased from -1.9 (-2.2, -1.7) at birth to -1.0 (-1.7, -0.5) at 2 year. In the intermediate tertile, median WAZ at birth and 2 year were similar [-1.0 (-1.2, -0.7) and -0.8 (-1.6, -0.1), respectively]; while for infants in the highest WAZ_0 tertile, the median WAZ decreased from 0.02 (-0.3, 0.4) at birth to -0.4 (-1.2, 0.3) at 2 year. Babies on either end of the WAZ_0 spectrum converged towards the median by 2 years (**Fig. 2).** Of the 12 SGA infants, catch-up growth was seen in 3 and 8 infants at 3.5 months and 2 years, respectively; while catch-down growth was seen in two infants at 3.5 months. Of the LGA infants, 17 (48.6%) infants under follow-up at 3.5 months experienced catch-down growth, while 4 (11.3%) had catch-up growth. By 2 years, 17 (47.2%) of the 36 LGA



LGA: Large for gestation age; SGA: Small for gestational age.

Fig. 1 Flow of participants in the study.

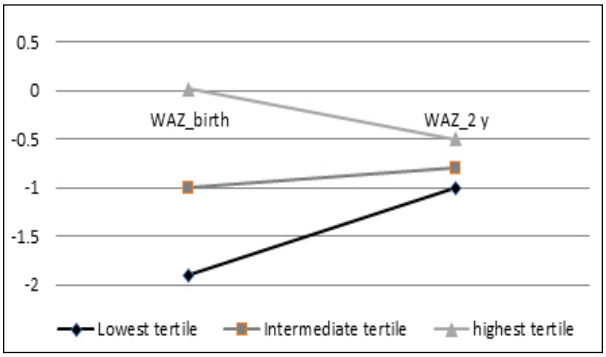


Fig. 2 Median weight for age Z- scores (WAZ) at birth and at 2 years in the infants in the three tertiles of WAZ at birth, illustrating the convergence towards the median (narrowing of the funnel).

Table II Anthropometric Parameters at Birth and Follow-up

Parameters	*Birth (n=262)*	*3.5 m (n=222)*	*1 y (n=231)*	*2 y (n=223)*
Weight, g[a]	2863 (418)	5587 (790)	8959 (1180)	10882 (1420)
WAZ[b]	-1.0 (-1.7, -0.3)	-1.2 (-1.8, -0.5)	-0.7 (-1.4, -0.1)	-0.8 (-1.5, -0.8)
WAZ <-2, *n* (%)	34 (13.0)	40 (18.0)	24 (10.4)	24 (10.8)
Length, cm[a]	48.4 (2.2)	61.0 (3.1)	75.1 (3.1)	84.1 (3.6)
LAZ[b]	-0.9 (-1.5, 0.03)	-0.2 (-1.8, 0.6)	-0.4 (-1.3, 0.3)	-0.9 (-1.4, -0.07)
LAZ <-2, *n* (%)	37 (14.3)	23 (10.5)	19 (8.3)	23 (10.4)
BMI, Kg/m^2[a]	12.2 (1.4)	14.9 (1.7)	15.9 (1.6)	15.4 (1.6)
BMIZ[b]	-0.9(-1.7, -0.2)	-1.3(-2.1, -0.5)	-0.7 (-1.4, 0.3)	-0.4(-1.3, 0.3)
BMIZ <-2, *n* (%)	53 (20.4)	64 (29.9)	22 (9.6)	18 (8.1)
BF%[c]	14.4 (3.4)	23.9 (3.1)	21.7 (3.2)	20.3 (2.8)

WAZ: Weight for age, LAZ: Weight for age: BMI: Body mass index; BMIZ: BMI for age; BF: Body fat. [a]mean (SD); [b]median (IQR).

Table III Catch-up and Catch-down Growth in Weight From Birth to 2 Years

	Infants with catch-up growth	*Infants with steady growth*	*Infants with catch-down growth*	*P value*
Between birth to 3.5 mo (n=222)				
n (%)	40 (18)	123 (55)	59 (27)	
Weight at birth, g	2659 (385)	2841 (380)	3016 (404)	<0.001
WAZ at birth	-1.6 (-2.1, -0.8)	-1.0 (-1.7, -0.4)	-0.6 (-1.2, 0.1)	<0.001
Weight at 3.5 mo, g	6148 (792)	5646 (691)	5083 (723)	<0.001
WAZ at 3.5 mo	-0.2 (-0.8, 0.2)	-1.1 (-1.6, -0.5)	-1.8 (-2.6, -1.3)	<0.001
Exclusively breastfed till 3.5 mo, %	63	74	47	0.006
Between birth to 1y (n=231)				
n (%)	95 (41)	78 (34)	58 (25)	
Weight at birth, g	2597 (294)	2898 (326)	3245 (337)	<0.001
WAZ at birth	-1.6 (-2.1, -1.0)	-0.8 (-1.4, -0.4)	-0.1 (-0.6, 0.5)	<0.001
Weight at 1 y, g	9751 (1123)	8723 (841)	7973 (708)	<0.001
WAZ at 1 y	0.2 (-0.5, 0.7)	-0.8 (-1.4, -0.4)	-1.6 (-2.0, -1.2)	<0.001
Caloric intake at 1 y, Kcal/d	835 (176)	818 (139)	874 (140)	0.186
Between birth to 2 y (n=223)				
n (%)	84 (38)	87 (39)	52 (23)	
Weight at birth, g	2641 (345)	2896 (376)	3113 (384)	<0.001
WAZ at birth	-1.6 (-2.0, -0.9)	-0.8 (-1.5, - 0.3)	-0.5 (-1.2, 0.1)	<0.001
Weight at 2 y, kg	11.7 (1.5)	10.7 (1.2)	9.9 (0.9)	<0.001
WAZ at 2 y	-0.1 (-0.5, 0.5)	-0.9 (-1.5, -0.3)	-1.6 (-2.3, -1.2)	<0.001
Caloric intake at 1 y, Kcal/d	869 (158)	830 (153)	811 (151)	0.120
Caloric intake at 2 y, Kcal/d	1045 (147)	998 (139)	913 (123)	<0.001

WAZ: Weight for age z score; LAZ: Weight for age z score; BMI: Body mass index; BMIZ: BMI for age z score; BF: Body fat; Weight and caloric intake in mean (SD); WAZ in median (IQR); Data was available for 177, 183 and 172 infants for duration of exclusive breastfeeding, caloric intake at 1 y and caloric intake at 2y, respectively.

infants in follow-up had catch-down growth, while 5 (13.9%) had catch-up growth.

Catch-up growth and catch-down growth in length between birth to 3.5 months was seen in 103 (47%) and 35 (16%) infants, at 1 year in 94 (41%) and 68 (28%) infants, and at 2 years in 67 (30%) and 73 (33%) infants, respectively. The mean (SD) birth length of those with catch-up between birth to 3.5 months was 47.5 (2.2) cm, those with steady growth was 48.7 (1.9) cm and those with catch-down was 49.9 (2.1) cm (P<0.001). Similarly, the mean (SD) birth length of those with catch-up growth between birth to 1 year, was 46.8 (1.9) cm compared to 48.9 (1.9) cm for those with steady growth, and 50.1 (1.6) cm for those with catch-down growth (P<0.001). Mean (SD) birth lengths were 46.7 (1.9) cm, 48.3 (1.7) cm and 50.0 (1.9) cm, respectively for those with catch-up growth, steady growth and catch-down growth between 0-2 years (P<0.001). A higher pro-portion of infants (39%) had catch-down growth in length in the second year compared to catch-up growth (23%).

Table IV compares the anthropometry and body fat percentage at birth and 2 years of age, and the nutritional intakes of infants who had early catch-up growth in weight (between birth to 3.5 months), intermediate catch-up growth (birth to 1 year), late/slow catch-up growth (birth to 2 years), and no catch-up growth in four mutually exclusive groups.

The increase in weight for age (ΔWAZ) between birth to 3.5 months was positively correlated with body fat percentage at 1 year (r=0.252, P<0.001) and at 2 years (r=0.154, P=0.030). Length for age z-score (LAZ) at birth showed positive correlation with birthweight (r=0.535, P<0.001), and mother's weight (r=0.142, P=0.026) but not with either parent's height. LAZ at 2 years strongly correlated with mother's height (r=0.211, P=0.002) as well as father's height (r=0.215, P=0.001).

Birthweight was inversely associated with ΔWAZ at 3.5 months (r= -0.349, P<0.001; and at 1 year (r=-0.663, P<0.001). ΔWAZ between first and second year was

Table IV Comparison of Anthropometric Parameters and Adiposity at Birth and 2 Year of Age and Nutrition of Infants With Different Patterns of Catch-up Growth

Parameter	*Early/ rapid CUG (n=40)*	*Intermediate CUG (n=76)*	*Slow/ late CUG (n=35)*	*No CUG (n=90)*
At birth				
Weight, g[a]	2659 (385)	2612 (281)	2788 (316)	3103 (380)
Weight-for-age *z*-score[b]	-1.5 (-2.1, -0.8)	-1.5 (-2.0, -1.0)	-1.0 (-1.6, -0.5)	-0.4 (-1.0, 0.2)
Length, cm[a]	48.3 (2.3)	47.4 (2.2)	47.9 (2.1)	49.4 (2.0)
Length-for-age *z*-score[b]	-1.0 (-1.6, -0.1)	-1.4 (-2.0, -0.2)	-1.0 (-1.4, -0.1)	-0.3 (-1.1, 0.3)
Body mass index, kg/m^2[a]	11.4 (3.5)	11.6 (1.2)	12.2 (1.0)	12.7 (1.3)
BMIZ[b]	-1.8 (-2.6, -0.8)	-1.4 (-2.1, -0.8)	-0.9 (-1.4, -0.5)	-0.5 (-1.1, 0.1)
Body fat %[a]	13.7 (3.5)	13.8 (3.5)	13.3 (2.8)	15.4 (3.1)
At 2 y				
Weight, kg[a]	10.9 (1.5)	10.6 (1.4)	12.4 (1.2)	10.6 (1.2)
Weight-for-age *z*-score[b]	-0.5 (-1.5, -0.1)	-1.0 (-1.7, - 0.4)	0.2 (-0.4, 0.7)	-1.1 (-1.6, -0.5)
Length, cm[a]	82.5 (4.3)	83.8 (3.8)	85.3 (3.7)	83.8 (3.2)
Length-for-age *z*-score[b]	-1.1 (-1.4, 0.1)	-1.0 (-1.5, -0.2)	-0.2 (-0.4, 0.7)	-1.0 (-1.5, -0.4)
Body mass index, kg/m^2[a]	16.0 (1.5)	15.1 (1.5)	16.7 (1.5)	15.1 (1.4)
BMIZ[b]	-0.2 (-0.9, 0.5)	-0.8 (-1.5, 0.2)	1.0 (0.9, 1.6)	-0.6 (-1.1,- 0.04)
Body fat, %[a]	20.9 (2.1)	20.1 (2.6)	22.0 (2.9)	19.5 (2.8)
Nutrition				
Duration of exclusive breastfeeding, mo[a]	4.7 (1.8)	4.5 (1.8)	4.4 (1.6)	4.4 (1.7)
Caloric intake at 1 y, Kcal/d[a]	838 (122)	842 (186)	846 (157)	839 (145)
Caloric intake at 2 y, Kcal/d[a]	1009 (141)	958 (141)	1069 (150)	978 (121)

CUG: Catch-up growth in weight; Early/rapid CUG: CUG between birth to 3.5 mo; Intermediate CUG: CUG between birth to 1 y; Slow/late CUG: CUG between birth to 2 y; No CUG between birth to 3.5 mo, 1 y or 2 y; BMIZ: BMI for age Z-score. [a]Mean (SD); [b]Median (IQR). P-value was <0.001 by ANOVA for all the group comparisons for anthropometry and body fat percentage; P-value=0.005 for comparison of caloric intake at 2 y; Data was available for 177 infants for duration of exclusive breastfeeding, 183 for caloric intake at 1 y, and 172 for caloric intake at 2 y.

positively associated with caloric intake assessed at 1 year (r = 0.172, P=0.024) and 2 years (r = 0.379, P<0.001). For ΔWAZ between birth and 2 years, the regression coefficients with birthweight and caloric intake at 2 years were -3.754 (P<0.001) and 0.003 (P<0.001), respectively, with adjusted R-squared of 0.72. Birthweight itself positively correlated with maternal weight (r=0.205, P<0.001) and height (r=0.157, P=0.013); and was higher in infants born to multiparous compared to primiparous mothers; 2954 (434) g vs 2776 (375) g; P<0.001, and in boys compared to girls; 2949 (438) g vs 2746 (360) g, P<0.001. Socioeconomic status, mothers' education, fathers' height and weight did not affect birth weight or ΔWAZ between any of the time points. In this cohort, 34% of the infants were exclusively breastfed for ≤3.5 months. The odds ratio (95% CI) for having CUG between birth and 2y was 1.8 (0.95-3.4), P=0.073, for infants who were exclusively breastfed for ≤3.5 months compared to those exclusively breastfed for a longer duration.

DISCUSSION

In this contemporary birth cohort, median weight and length *z*-scores were close to –1 at birth, improved by one year of age and again declined during the second year. Body fat percentage increased maximally between birth to 3.5 months, and then showed a small decline.

Both catch-up growth and catch-down growth in weight were common in this cohort. Infants with birthweight close to the median birthweight of Indian infants (approximately 2.9 kg) had a steady growth pattern while those with lower and higher birthweights showed catch-up growth and catch-down growth patterns, respectively. A similar pattern was noted for length, with the median length of infants with steady growth being about 48.5 cm, which is close to our national average. Catch-up growth and catch-down growth are considered as target-seeking patterns that bring babies with fetal growth restriction and excessive fetal growth,

WHAT IS ALREADY KNOWN?

- Infants with low birthweight experience catch-up growth in the first two years.

WHAT THIS STUDY ADDS?

- Both catch-up and catch-down growth in weight and length are common in the first 2 years in healthy term infants.

respectively, towards their normal growth channels [10]. Thus, the present study suggests that the birthweight and length of Indian babies, although low as compared to the international median [1], may be physiologically normal for our population. Similar conclusions were drawn in a previous study from southern India that noted that birthweight distribution of Indian infants is shifted to the left, and the risks associated with being LGA were present at lower weights [17].

The weight trajectories of infants born in the lowest and highest tertile of WAZ converged at 2 years like narrowing of a funnel, similar to observations in Bangladeshi infants [18]. In the present study, LAZ at 2 years but not at birth correlated with the height of both parents. Thus, CUG and CDG in length served to align the length of the infants to their genetic potential. About two-thirds of infants cross length centiles in the first 2 years in order to reach their mid-parental height centiles [19].

In the present study, weight CUG between birth and 3.5 month, 1 year and 2 year was chiefly driven by lower birthweight. Previous studies have also emphasized that lower birthweight is the exclusive determinant of CUG in first six months [20]; and growth during infancy should be assessed not just by comparing with reference charts, but also taking infants' birthweights into account [21]. In the present study, it was observed that while catch-up growth was commoner than catch-down in the first year, the reverse was true in the second year; and change in weight *z*-score between 1-2 year was positively correlated with caloric intake. An earlier Indian study [22] reported an inverse association between duration of exclusive breastfeeding and weight gain between birth to 2 years, similar to the present study, reiterating that optimal feeding between birth to 2 years is important to avoid growth faltering as well as accelerated weight gain.

The mean values of body fat percentage in the present study were similar to those reported from the Western countries [15,16]. An overall trend for improvement in nutritional status was observed in this study, more marked for BMI than length.

Infants who had catch-up growth in first 3.5 months had higher BMI *z* scores and body fat at 2 years compared to those without catch-up growth. The median LAZ remained nearly the same, indicating that early weight catch-up growth does not improve statural growth but may contribute to obesity in later childhood. These findings were in consonance with our earlier study where early catch-up growth (in first 6 to 12 weeks) in term low birth infants was associated with higher body fat at 7 months [23]. Rapid weight gain in early infancy may contribute to later adiposity, obesity and cardiometabolic diseases [2-7].

This study used WHO *z*-scores for presenting the anthropometric data, which takes into account the variations in the exact age at the time of anthropometric measurements as well as gender, and makes international comparisons easier. The study had low attrition, and we also measured body fat. The limitations were that the findings cannot be extrapolated to infants with birth weights outside the 1800-4000 g range, the effect of catch-up growth and catch-down growth on neurodevelopment, risk of infections, blood pressure and metabolic parameters was not assessed, and longer follow-up of this cohort was not done.

To conclude, catch-up and catch-down growth in weight and length are very common in the first 2 years of life, which may represent physiological adjustments towards the median and the genetically determined growth trajectory in the majority. Infants' feeding may also contribute to growth acceleration/deceleration. Early increase in weight *z*-score was associated with higher adiposity at the age of 1 and 2 years. We recommend that the determinants and consequences of CUG and CDG in infancy should be studied further in larger cohorts followed up for a longer duration.

Acknowledgments: Babita Upadhyaya, dietician, for help with dietary assessment, and Anuj Kumar and Naveen Kumar for technical help with acquisition of data.

Ethics clearance: AIIMS Ethics Committee; No. IEC/NP-127/2012 and RP-21/2012, dated April 27, 2012.

Contributors: VJ: conceptualized and designed the work, supervised data acquisition and analysis, interpreted the data and drafted the paper; BK, SK: acquired the data and helped with analysis and writing. All authors have given final approval to the

version to be published.
Funding: Department of Biotechnology, Government of India (Grant No. BT/PR3884/Med/97/03/2011).
Competing interests: None stated.

REFERENCES

1. Villar J, Cheikh Ismail L, Victora CG, et al. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384: 857-68.
2. Jain V, Singhal A. Catch up growth in low birth weight infants: Striking a healthy balance. Rev Endocr Metab Disord. 2012;13:141-7.
3. Weaver LT. Rapid growth in infancy: balancing the interests of the child. J Pediatr Gastroenterol Nutr. 2006; 43:428-32.
4. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: Prospective cohort study. BMJ. 2000;320:967-71.
5. Aris IM, Chen LW, Tint MT, et al. Body mass index trajectories in the first two years and subsequent childhood cardio-metabolic outcomes: A prospective multi-ethnic Asian cohort study. Sci Rep 2017;7:8424.
6. Fall CH, Sachdev HPS, Osmond C, et al. New Delhi Birth Cohort. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of BMI gain during infancy: Data from the New Delhi Birth Cohort. Diabetes Care. 2008;31:2349-56.
7. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA. 2009;301: 2234-42.
8. Kim R, Mejía-Guevara I, Corsi DJ, Aguayo VM, Subramanian SV. Relative importance of 13 correlates of child stunting in South Asia: Insights from nationally representative data from Afghanistan, Bangladesh, India, Nepal, and Pakistan. Soc Sci Med. 2017;187:144-54.
9. Völkl TM, Haas B, Beier C, Simm D, Dörr HG. Catch-down growth during infancy of children born small (SGA) or appropriate (AGA) for gestational age with short-statured parents. J Pediatr. 2006;148:747-52.
10. Tanner JM. Growth from birth to two: A critical review. Acta Medica Auxologica. 1994: 26:7-45.
11. Singhal PK, Paul VK, Deorari AK, Singh M, Sundaram KR. Changing trends in intrauterine growth curves. Indian Pediatr. 1991;28:281-3.
12. Bairwa M, Rajput M, Sachdeva S. Modified Kuppuswamy's socioeconomic scale: Social researcher should include updated income criteria, 2012. Indian J Community Med. 2013;38:185-6.
13. Weststrate JA, Deurenberg P. Body composition in children: Proposal for a method for calculating body fat percentage from total body density or skinfold-thickness measurements. Am J Clin Nutr. 1989;50:1104-15.
14. WHO/UNICEF/USAID/AED/FANTA/UC Davis/IFPRI. Indicators for Assessing Infant and Young Child Feeding Practices. Part II. Measurement. 2010. Accessed November 07, 2019. Available from: *https://www.who.int/nutrition/publications/infantfeeding/9789241599290/en/*
15. Schmelzle HR, Fusch C. Body fat in neonates and young infants: validation of skinfold thickness versus dual-energy *X*-ray absorptiometry. Am J Clin Nutr. 2002;76:1096-100.
16. Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. Body composition during the first 2 years of life: An updated reference. Pediatr Res. 2000;47:578-85.
17. Alexander AM, George K, Muliyil J, Bose A, Prasad JH. Birth weight centile charts from rural community-based data from Southern India. Indian Pediatr. 2013;50:1020-4.
18. Karim E, Mascie-Taylor CG. Longitudinal growth of Bangladeshi infants during the first year of life. Ann Hum Biol. 2001;28:51-67.
19. Brooke OG, Wood C. Growth in British Asians: Longitudinal data in the first year. J Hum Nutr. 1980;34: 355-9.
20. Davies DP. Growth of "small-for-dates" babies. Early Hum Dev. 1981;5:95-105.
21. Xiong X, Wightkin J, Magnus JH, et al. Birth weight and infant growth: Optimal infant weight gain versus optimal infant weight. Matern Child Health J. 2007;11:57-63.
22. Caleyachetty A, Krishnaveni GV, Veena SR, et al. Breastfeeding duration, age of starting solids and high BMI risk and adiposity in Indian children. Matern Child Nutr 2013; 9:199-216.
23. Khandelwal P, Jain V, Gupta AK, Kalaivani M, Paul VK. Association of early postnatal growth trajectory with body composition in term low birth weight infants. J Dev Orig Health Dis. 2014;5:189-96.

RESEARCH PAPER

Situational Analysis of Management of Childhood Diarrhea and Pneumonia in 13 District Hospitals in India

HARISH KUMAR,[1] ASHFAQ AHMED BHAT,[2] VARUN ALWADHI,[3] RAJAT KHANNA,[2] SUTAPA B NEOGI,[4] AJAY KHERA[5] AND SILA DEB[5]

[1]Vriddhi, IPE Global Ltd., New Delhi, India; [2]Norway India Partnership Initiative, New Delhi, India; [3]Kalawati Saran Children Hospital, New Delhi, India; [4]International Institute of Health Management Research, New Delhi, India; and [5]Ministry of Health and Family Welfare, Government of India, New Delhi, India.

Correspondence to: Dr Ashfaq Ahmed Bhat, Norway India Partnership Initiative, New Delhi, India. bhatashfaq@gmail.com

Received: May 08, 2019; Initial review: October 04, 2019; Accepted: September 28, 2020.

Objective: To generate evidence on the current situation of hospital care (emergency, inpatient and outpatient), for managing children presenting with diarrhea and pneumonia at 13 district hospitals in India.

Design: Facility-based assessment of district hospitals.

Settings: 13 district hospitals in four states of Bihar, Madhya Pradesh, Odisha and Rajasthan.

Participants: Staff nurses and doctors.

Intervention: None.

Methods: An assessment was done across 13 district hospitals in four states by a group or trained assessors using an adapted quality assurance tool developed by Government of India where each aspect of care was scored (maximum score 5). Emergency services and triage, case management practices, laboratory support, and record maintenance for diarrhea and pneumonia were assessed.

Results: Separate diarrhea treatment unit was not earmarked in any of the DHs surveyed. Overall score obtained for adequate management of diarrhea and pneumonia was 2 and 2.2 which were poor. Pediatric beds were 6.8% of the total bed strength against the recommended 8-10%. There was a 65 percent shortfall in the numbers of medical officers in position and 48 percent shortfall of nurses. There were issues with availability and utilization of drugs and equipment at appropriate places with cumulative score of 2.8. Triage for sick children was absent in all the facilities.

Conclusion: The standards of pediatric care for management of diarrhea and pneumonia were far from satisfactory. This calls for improvement of pediatric care units and implementation of operational guidelines for improving management of diarrhea and pneumonia.

Keywords: *Assessment, Childhood illness, Operational guidelines*, *Quality assurance.*

Published online: January 02, 2021; ***PII*:** S097475591600272

Newborn conditions, diarrhea and pneumonia contribute to nearly 79.4% of deaths in Indian children under five years of age [1]. The Integrated Global Action Plan for Prevention and Management of Pneumonia and Diarrhoea (GAPPD), 2013 includes treatment of sick children at health facilities as an integral component of the three pronged approach (protect, prevent, and treat) [2].

Delivery of good quality facility-based healthcare can reduce childhood deaths in low and middle-income countries where mortality is high. Both anecdotal and empirical evidence suggest that the quality of services can be improved only when it is reliably measured [3-5]. Various studies of the quality of services given to children in developing countries have highlighted deficiencies in practice of pediatric clinical guidelines, health worker training, triage and emergency treatment systems, staffing, monitoring, inadequate supportive care, essential equipment and medication [5-7]. A qualitative study in 13 district hospitals and eight teaching hospitals in seven less-developed countries highlighted that 14 of 21 hospitals lacked an adequate system for triage. Initial patient assessment was often inadequate and treatment delayed [8].

Editorial commentary: Pages 313-14

In India, as an adaptation of GAPPD, the Government of India (GoI) along with WHO and UNICEF developed an Integrated Action Plan for Pneumonia and Diarrhea (IAPPD) [9] in September, 2014 . The district hospital (DH) is positioned in this continuum as second referral health facility, which provides specialist care under National Health Mission (NHM). The DH is envisaged as the hub of effective curative care for children, including those in age group 0-5 years, for common morbidities like diarrhea and pneumonia.

There is a dearth of evidence on the current situation

of hospital care (emergency, inpatient and outpatient) for managing children presenting with diarrhea and pneumonia at DHs in India. Norway India Partnership Initiative (NIPI), launched in 2006, was a collaborative effort between Governments of Norway and India to support the NHM by providing strategic and catalytic support, and by testing scalable health system innovations. As part of this initiative, a comprehensive assessment was conducted across five states that highlighted gaps in the basic requirements for delivering effective pediatric care. The current study aims to assess the secondary health facilities (district hospitals) for provision of services with focus on management of diarrhea and pneumonia as part of Facility-based Integrated Management of Neonatal and Childhood Illness (F-IMNCI).

METHODS

This cross sectional study was undertaken as part of NIPI newborn project in May, 2014 across DHs of 13 implementation districts in four states under the project (2013-2017) that contribute to maximum childhood mortality: Bihar, Odisha, Madhya Pradesh and Rajasthan. The districts had a total population of more than two crores with an estimated under five population of 27 lakhs, and 4.82 lakh estimated live births each year.

A team of trained doctors (assessors) oriented on the protocol visited the hospital after prior information. Cases were observed to assess clinical management of children admitted to hospitals with diarrhea and pneumonia during the visit. This was also complemented by a review of case records. Observations were largely focused on understanding delivery of standard care for diarrhea and pneumonia, as information was inadequate in patient records. Clarifications were sought from doctors and nurses wherever required. Mothers/caregivers were also interviewed.

The assessment tool was adapted from the quality assurance tool developed by the Ministry of Health and Family Welfare (MoHFW), GoI [10]. It comprised of 12 sections including general hospital information, hospital support systems, organization of the emergency care and children's ward, case management of childhood diseases, supportive care, monitoring and hospital administration. Each section included a range of questions including those pertaining to case management. Scores were given based on whether the DH met the national standards for management of diarrhea and pneumonia, as detailed under F-IMNCI. Provisions were made to record personal observations if any. The adequacy of bed strength were assessed by Indian Public Health Standards according to which 300 beds should be available for 10 lakh population. Similarly, adequacy of number of medical officers, pediatricians and nurses were also assessed [11].

Scoring from 1 to 5 for each point was done comparing with standard of care, where 1 was for services not provided, totally inadequate care or potentially life-threatening practices requiring urgent improvement, 2 for considerable need for improvement, 3 for some need for improvement, 4 for little need for improvement, and 5 for good practice complying with standards of care. Summary scores of all DHs were calculated for a cumulative score.

Data were collected on paper forms. Completed assessment tools from all the assessors were received at the state and national offices of UNDP-NIPI newborn project and scrutinized for data discrepancy by the monitoring and evaluation unit. Data were entered and compiled at state and national offices in a Microsoft Excel format. SPSS was used for analysis of data.

Approval for health facility assessment and data collection was obtained from MoHFW, GoI and the state governments. Since quality assurance is part of the government policy, ethical approval for this particular activity was not sought from any ethics committee. However, the identity of staff and care givers interviewed during the assessment was kept confidential and personal identifiers were not recorded. Appropriate feedback was given to the district and state authorities after the assessment.

RESULTS

All 13 districts had a functioning DH with number of beds ranging from 100 to 487. A total of 3171 functional hospital beds were available with 216 (6.8%) paediatric beds. Additional 76 beds in nutritional rehabilitation centres and 155 beds in sick newborn care units were also available. The total bed strength at DHs fell short by 50%. There was a 65% shortfall in the numbers of medical officers in position and 48% shortfall of nurses. A 36% shortfall of pediatricians was recorded, which would be higher after accounting for pediatricians who were allocated to other units simultaneously. Only six pediatricians were trained in F-IMNCI, two medical officers were trained in advanced life support, and none of the other staff working in emergency department were trained in Emergency Triage and Treatment (ETAT). However, all children were attended by atleast MBBS doctors.

All the four DHs in Madhya Pradesh had continuous electricity supply and power backup was available only in emergency and not the pediatric wards or OPDs in Rajasthan, Odisha and Bihar. Running water was

Table I Cumulative Score of Quality of Service in 13 District Hospitals (*N*=13)

Service	*Bihar*			*Madhya Pradesh*			*Rajasthan*			*Odisha*			*Average*
	Jehanabad	*Nalanda*	*Sheikhpura*	*Hoshangabad*	*Betul*	*Narsinghpur*	*Raisen*	*Alwar*	*Bharatpur*	*Dausa*	*Angul*	*Jharsuguda Sambalpur*	
Essential drugs, equipment and supplies	2	2	2	3	3	3	3	4	4	3	3	3	2.8
Laboratory support	1	3	1	3	3	3	3	3	3	3	2	3	2.5
Emergency care	1	2	1	2	3	2	2	2	2	3	2	2	2.0
Children's ward and facilities	1	2	1	3	3	2	3	3	3	2	3	3	2.4
Cough and difficult breathing	1	1	1	2	3	2	2	3	3	3	3	2	2.2
Management of diarrhea	1	1	1	2	2	2	2	3	3	3	2	2	2.0
Supportive care	1	2	1	3	3	2	2	2	2	2	3	3	2.2
Monitoring	1	1	1	2	3	2	2	2	2	2	3	2	1.9
Hospital administration	2	2	2	3	3	3	3	2	3	2	2	3	2.4
Access to hospital care	2	2	1	2	3	3	3	3	2	3	3	3	2.5

Maximum score= 5 for each point.

available round-the-clock in nine districts in the emergency, while only seven had running water available in pediatric ward. Biomedical waste management was inadequate across DHs, more so in Rajasthan and Bihar, where all the DHs lacked proper segregation of waste.

Laboratory support was available across all DHs, except one. The existing laboratory services needed improvement in terms of round-the-clock availability and the range of diagnostic tests performed. All DHs were found to be providing inadequate supportive care as shown in **Table I**. There were no major financial barriers with regard to the availability of essential drugs and transportation. However, caregivers were not aware of the provision of free transportation facilities for sick newborns and infants from home to health facility (under JSSK scheme). Referral transport was most often used for referrals between health facilities than for transport of sick children from home to health facility.

Separate pediatric wards were present in 12 out of 13 DHs surveyed. None of the DHs had a system for triage for sick children, though they had a separate area/department for managing emergencies. Staffing of emergency department in all DHs was limited to one medical officer and one nurse in each of the three shifts.

The performance of DHs in management of pneumonia and diarrhea are shown in **Table II**. Irrational use of antibiotics, corticosteroids, sedatives and antihistamines was evident; use of third generation cephalosporin was common instead of penicillin derivatives plus aminoglycoside combination, as recommended. Nebulizers and salbutamol respiratory solution were available in pediatric ward in seven and five DHs, respectively; however, their use was not observed during the visit. Regular monitoring of admitted patients and records of examined patients were not maintained for cross verification. In nine DHs, most of the admitted children were administered IV fluids, even when not indicated, and used as a calorie source beyond initial phase of stabilization.

None of the DHs had a separate area or Diarrhea Treatment Unit (DTU) or provision for performing tests for electrolytes (sodium and potassium levels) or stool culture. Dehydration was not correctly assessed or recorded. Use of ORS in children admitted to DH was not observed and intravenous fluids were being administered to all children. Interviews with mothers revealed that feeding history was not assessed and advised. Age-appropriate food was not served to sick inpatient children in five DHs. Records of inpatients for clinical progress, monitoring, feeding or medications administered were not maintained. Standard patient record formats were not

Table II Performance of District Hospitals in the Management of Pneumonia and Diarrhea (*N*=10)*

Standards and criteria for management	*No. of facilities to be improved*
For cough or difficult breathing	
Severity of pneumonia is correctly assessed and diagnosed.	9
Appropriate antibiotics are administered for pneumonia and other respiratory diagnoses	9
Oxygen is correctly administered when necessary	9
Correct use of chest *X*-ray	6
Appropriate diagnosis and management of TB	5
Inhaled bronchodilators are given appropriately when indicated	8
Patient monitoring appropriately performed and charted	9
Supportive care provided appropriate for condition	9
For diarrhea	
Dehydration is correctly assessed	10
Rehydration plan is appropriate to severity of dehydration, and appropriately monitored	10
Appropriate antibiotics only given when necessary	10
Antidiarrheal drugs not given	6
Zinc used for managing diarrhea	6
Appropriate (continued) feeding given during diarrhea	5
Corticosteroids are only given for a clear indication	5

**Data not included for Jehanabad, Nalanda, and Sheikhpura as there were no inpatients.*

used or remained uncharted. Re-assessment of a child admitted during routine hours by a doctor was unlikely. Nutritional assessment was not undertaken in outpatients and inpatients routinely, therefore there were few referrals or admissions to nutritional rehabilitation centers (co- located at DH at many sites).

DISCUSSION

An assessment of 13 DHs in four states showed that the basic infrastructure for managing cases of diarrhea and pneumonia and supportive services were present with shortage of human resources. Cumulative score for each service component across every facility was less than satisfactory with deficits in clinical case management, record maintenance and triage.

There were certain limitations on the assessment of DHs for management of pediatric diarrhoea and pneumonia. We did not consider all the elements of quality of health care viz. effectiveness, safety, people centricity, timeliness, equity, integrated services and efficiency, since this was beyond the scope of the assessment and the tool used. Direct observation of admitted cases was carried out but ongoing evaluation as outlined in the F-IMNCI protocol could not be done due to logistic issues. The skills of doctors and nurses were not assessed. The study was restricted to 13 DHs in high burden states; hence, generalizability of findings across all settings becomes difficult.

The assessment findings are comparable to the evidence generated from other low and middle income countries (LMICs) [5,7,8,12]. Shortage of beds was reported consistently from all sites in the present study, which is likely to influence the patient outcomes [13]. Many DHs run by under-resourced non-government organizations like in remote parts of Papua New Guinea [12] and sub-district hospitals in Bangladesh [5], have general wards to house both adults and children together, unlike most DHs in the present assessment. Assessment of emergency services in primary and secondary level facilities indicate the strength and efficiency of the health system [14]. A functional triage seems to be a challenge in many hospitals in LMICs [4,5]. Similarly, none of the DHs had DTU that is a requirement as laid down by facility-based pediatric operational guidelines [15]. The absence of these facilities is likely to compromise with the quality of services and can be related to poor outcomes such as mortality.

Case management practices from LMICs highlight certain challenges, similar to the findings that have emerged from our assessment. Inadequacies were seen in key tasks such as prescription of antibiotics and feeds even when resources were made available and guidelines provided [5,16]. This could be because of gaps in skill building of staff as also seen in experience from Papua New Guinea [12] and Malawi [16]. Quality of services for pneumonia was better in urban hospitals in Rwanda compared to rural hospitals [7]. In a similar nation-wide study conducted on case management of pneumonia in DHs in Malawi, case management guidelines were poorly implemented with frequent interruptions in the supply of antibiotics, oxygen, and lack of a reporting system [8]. Availability of essential drugs was seen to be a challenge in Bangladesh [5] similar to our study.

Documentation of clinical management remains a challenge in the assessment of DHs. A retrospective record review from Kenya showed missed outcome details in 20% of the admissions [19]. Clinical documentation of signs and symptoms was also poor in eight DHs in Kenya [16]. Training of staff on ETAT and management of diarrhoea and pneumonia resulted in improvement of practices and implementation of guidelines but documentation remained poor [20]. Even with minimum investment, triage based on the risk scores can

WHAT THIS STUDY ADDS?

- Standards and quality of services were found to be unsatisfactory in 13 district hospitals across four states in India with need to upscale manpower and training of healthcare providers.

inform decisions [21]. With no additional investment of material resources, face to face feedback of performance, supportive supervision and provision of a local facilitator resulted in improvements of pediatric care and the readiness for providing care at DHs [22]. In most countries, academic rigour is directed towards clinical care in tertiary university hospitals with inadequate attention to peripheral hospitals, which are understaffed, poorly equipped and maintained, and have limited staff training [23].

To conclude, the assessment showed that standards of care for management of diarrhea and pneumonia were far from being met. It calls for planning and systematic implementation of the following recommendations: establishment of pediatric triage in all districts hospitals to facilitate rational management depending on the severity of diarrhea and pneumonia, based on national standards and operational guidelines, development of skills of doctors and nurses to manage pediatric emer-gencies (ETAT), management of diarrhea and pneumonia as per national standards of care (F-IMNCI); improve-ment of record keeping for pediatric services, both inpatient and outpatient, and introduction of standard patient record formats.

Contributors: HK: conceptualized the study and provided overall guidance; AAB,VA: guided the data compilation and supervised different steps involved in the study; RK: compiled and analyzed data of the assessment and supported the drafting of manuscript; SBN: reviewed the literature and drafted the manuscript; HK, AAB, AK, SD: technical inputs in finalizing the manuscript. All the authors have approved the final version of the manuscript.
Funding: Norway India Partnership Initiative (NIPI).
Competing interest: None stated.

REFERENCES

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: An updated systematic analysis. Lancet. 2015;385:430-40.
2. Chan M, Lake A. Integrated action for the prevention and control of pneumonia and diarrhoea. Lancet. 2013;381: 1436-7.
3. Ntoburi S, Hutchings A, Sanderson C, Carpenter J, Weber M, English M. Development of paediatric quality of inpatient care indicators for low-income countries - A Delphi study. BMC Pediatr. 2010;10:90.
4. Hategeka C, Mwai L, Tuyisenge L. Implementing the Emergency Triage, Assessment and Treatment plus admission care (ETAT+) clinical practice guidelines to improve quality of hospital care in Rwandan district hospitals: healthcare workers' perspectives on relevance and challenges. BMC Hlth Services Res. 2017;17:256.
5. Hoque DME, Rahman M, Billah SM, et al. An assessment of the quality of care for children in eighteen randomly selected district and sub-district hospitals in Bangladesh. BMC Pediatr. 2012;12:197.
6. Campbell H, Duke T, Weber M, et al. Global initiatives for improving hospital care for children: state of the art and future prospects. Pediatrics. 2008;121:e984-e92.
7. Hategeka C, Shoveller J, Tuyisenge L, Kenyon C, Cechetto DF, Lynd LD. Pediatric emergency care capacity in a low-resource setting: An assessment of district hospitals in Rwanda. PLoS One. 2017;12:e0173233.
8. Nolan T, Angos P, Cunha AJ, et al. Quality of hospital care for seriously ill children in less-developed countries. Lancet. 2001;357:106-10.
9. Ministry of Health and Family Welfare. India Newborn Action Plan (INAP) New Delhi: Ministry of Health and Family Welfare; 2013 [cited 2019 Feberuary 12].
10. Ministry of Health and Family Welfare. Operational guidelines for Quality Assurance in public health facilities New Delhi. 2013 [cited 2019 July 15].
11. Directorate General of Health Services. Indian Public Health Standards (IPHS)- Guidelines for District Hospitals New Delhi 2012. [cited 2019 March 3].
12. English M, Esamai F, Wasunna A, et al. Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. Lancet. 2004;363:1948-53.
13. Muzigaba M, Van Wyk B, Puoane T. Management of severe acute malnutrition in children under 5 years through the lens of health care workers in two rural South African hospitals. African J Prim Hlth Care Family Med. 2018; 10:e1-e8.
14. Solnes Miltenburg A, Kiritta RF, Bishanga TB, van Roosmalen J, Stekelenburg J. Assessing emergency obstetric and newborn care: can performance indicators capture health system weaknesses? BMC Preg Childbirth. 2017; 17:92.
15. Ministry of Health and Family Welfare. Strengthening Facility Based Paediatric Care. Accessed on February 12, 2019. Available from Government of India; 2015.
16. Gathara D, Opiyo N, Wagai J, et al. Quality of hospital care for sick newborns and severely malnourished children in Kenya: a two-year descriptive study in 8 hospitals. BMC health services research. 2011;11:307.
17. Hategeka C, Shoveller J, Tuyisenge L, Lynd LD. Assessing process of paediatric care in a resource-limited setting: A cross-sectional audit of district hospitals in Rwanda. Paediatr and Int Child Hlth. 2018;38:137-45.
18. Enarson PM, Gie RP, Mwansambo CC, et al. Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management. PLoS

One. 2014;9:e102955-e.
19. Menge I, Esamai F, van Reken D, Anabwani G. Paediatric morbidity and mortality at the Eldoret District Hospital, Kenya. East African Med. J. 1995;72:165-9.
20. Irimu GW, Gathara D, Zurovac D, et al. Performance of health workers in the management of seriously sick children at a Kenyan tertiary hospital: before and after a training intervention. PloS One. 2012;7:e39964-e.
21. Mpimbaza A, Sears D, Sserwanga A, et al. Admission risk score to predict inpatient pediatric mortality at four public hospitals in Uganda. PLoS One. 2015;10:e0133950-e.
22. Ayieko P, Ntoburi S, Wagai J, et al. A multifaceted intervention to implement guidelines and improve admission paediatric care in Kenyan district hospitals: A cluster randomised trial. PLoS Med. 2011;8:e1001018-e.
23. Duke T, Tamburlini G. Improving the quality of paediatric care in peripheral hospitals in developing countries. Arch Dis Childhood. 2003;88:563-5.

CLIPPINGS

Multi system inflammatory syndrome-children (MIS-C) Management (*WHO/2019-nCoV/Sci_Brief/Multisystem_Syndrome_Children*)

Management of MIS-C includes Immuno-modulatory, antiplatelet and anticoagulation therapy, Cardiac and Supportive management. A stepwise progression of immunomodulatory therapies should be used with IVIG (2 gm/kg) considered first tier therapy. Low moderate dose glucocorticoids (1-2 mg/kg/day) should be given with IVIG as adjunctive therapy if shock and/or organ threatening disease present.

In patients not responding to IVIG and low moderate dose glucocorticoids, high dose, IV pulse glucocorticoids (10 30 mg/kg/day) may be considered. Anakinra (4 mg/kg/day IV or SQ) may be considered for treatment of MIS C refractory to IVIG and glucocorticoids. Anticoagulant anti platelet therapy in MIS-C includes low dose aspirin (3-5 mg/kg/day; max 81 mg/day) , continued until normalization of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis. Patients with abnormal BNP and/or troponin T at diagnosis should have these laboratory parameters trended over time until they normalize. ECGs should be performed at a minimum of every 48 hours in hospitalized patients and during follow up visits. Echocardiograms should be repeated at a minimum of 7-14 days and 4-6 weeks after presentation. Patients with left ventricular (LV) dysfunction and/or CAA will require more frequent echocardiograms.

Lung-protective ventilation in pediatric acute respiratory syndrome (PARDS) *(Pediatr Allergy Immunol Pulmonol. 2019.35-44)*

The goals of ARDS management are to treat the underlying cause, provide adequate oxygenation and ventilation, and protect the lungs from ventilator-induced lung injury (VILI). The aims of lung-protective ventilation are to avoid overdistension (volutrauma and barotrauma), minimize atelectrauma and minimize biotrauma.

Standard of care for mechanical ventilation in the PICU is generally consistent with the ARDS Network study, and the PALICC guidelines recommend tidal volumes of 3–6 and 5–8 mL/kg for patients with poor and more preserved respiratory compliance, respectively, along with limiting inspiratory plateau pressure to 28 cm H2O.

PALICC strongly recommends the use of PEEP up to 15 cm H2O or greater for severe PARDS. To minimize the potential toxicity of ventilatory support required to oxygenate and ventilate PARDS patients, permissive hypoxemia and hypercapnia should be considered. PALICC also recommends oxygen saturation goals of 92%–97% for mild PARDS and 88%–92% and PEEP >10 cm H2O for severe PARDS.

PALICC recommendations include considering permissive hypercapnia for moderate to severe PARDS to minimize VILI, maintaining pH 7.15–7.30 using lung-protective strategies.

CN RAGHUNATH
raghu.picu@gmail.com

RESEARCH PAPER

Catalytic Support for Improving Clinical Care in Special Newborn Care Units (SNCU) Through Composite SNCU Quality of Care Index (SQCI)

HARISH KUMAR,[1] RAJAT KHANNA,[2] VARUN ALWADHI,[3] ASHFAQ AHMED BHAT,[2] SUTAPA B NEOGI,[4] PRADEEP CHOUDHRY[2], PRASANT KUMAR SABOTH[1] AND AJAY KHERA[5]

From [1]VRIDDHI, IPE Global Ltd.; [2]Norway India Partnership Initiative; [3]Department of Pediatrics, Kalawati Saran Children's Hospital; [4]International Institute of Health Management Research; and [5]Ministry of Health and Family Welfare, Government of India; New Delhi, India.

Correspondence to: Dr Ashfaq Ahmed Bhat, Norway India Partnership Initiative, New Delhi, India. bhatashfaq@gmail.com

Received: April 30, 2020; Initial review: June 29, 2020; Accepted: November 17, 2020.

Objective: To develop a composite index that serves as a proxy marker of quality of clinical service and pilot test its use in 11 special neonatal care units (SNCUs) across two states in India.

Design: Secondary data from SNCU webportal.

Settings: Special new-born care units in Rajasthan and Orissa.

Intervention: We developed a composite SNCU Quality of care Index (SQCI) based on seven indices from SNCU online database. These included rational admission index, index for rational use of antibiotics, inborn birth asphyxia index, index for mortality in normal weight babies, low birth weight admission index, low birth weight survival index, and optimal bed utilization index.

Outcome: Based on the SQCI score, the performance of SNCUs was labelled as good (SQCI 0.71- 1.0), satisfactory (SQCI 0.4-0.7) or unsatisfactory (SQCI <0.4).

Results: The mean difference in SQCI between Jan-Mar 2016 and 2017 was 0.20 (95% CI 0.13- 0.28; *P*<0.001). Similar results were obtained for rational admission index, rational use of antibiotics, mortality in normal weight babies, low birth weight survival and optimal bed utilization. A significant improvement in the overall composite score was noted in Odisha (Mean difference 0.22, 95% CI 0.11-0.33, *P*=0.003) and Rajasthan (Mean difference 0.17, 95% CI 0.05- 0.3, *P*=0.002). **Conclusion:** QI approach using SQCI tool is a useful and replicable intervention. Preliminary results show that it does lead to strengthening of implementation of the programs at SNCUs based on the comprehensive scores generated as part of routine system.

Keywords: *District hospital, Health programs, Health system, Quality improvement.*

India has experienced a rapid expansion of Facility Based Newborn Care (FBNC) at various levels in the health system in the last decade. The services provided at each level is a product of infrastructure, availability of skilled manpower, capacity of the institution and referral mechanisms available. The facilities have been classified as newborn care corners (NBCC) at every point of child birth, newborn stabilization units (NBSUs) at first referral units (FRUs) and special newborn care units (SNCUs) at district hospitals [1]. Ministry of Health and Family Welfare (MoHFW), Government of India (GoI) under National Health Mission (NHM) has ensured functional SNCUs, in most of the District Hospitals in the country and has plans to further strengthen these units [2,3].

The SNCUs are equipped to manage small and sick neonates except those who need mechanical ventilation and surgical care. These units have admission and discharge criteria for optimal utilization of services and bed strength and services [4]. SNCUs have resulted in improvement in case fatality among newborns admitted to hospitals [5]. However, there are challenges in infrastructure, manpower and care practices [6]. There is a need to assess the performance of SNCUs with respect to quality of patient care, organization and process to support improvement and enhance accountability [5,7-9].

Editorial commentary: Pages 313-14

Experiences from QI programs on FBNC are also limited [10-13]. Reports have uncovered the insufficiencies of data management systems to monitor key indicators. To address this gap, GoI with support from UNICEF and Norway India Partnership Initiative (NIPI) established a web-based data management and tracking system, 'SNCU online' in the year 2011, to be used across all the SNCUs in India. Between April, 2016 and March, 2017, SNCU online was functional in 571 SNCUs across 27 states with data available for more than 700,000 infants.

Measurement of quality of clinical services rendered in the SNCUs is essential for feedback and improvement. The objective of this study was to develop a composite index that serves as a proxy marker of quality of clinical service and pilot test its use in SNCUs in India.

METHODS

This study was conducted in two stages/phases viz., development of a composite index (SNCU Quality of Care Index or SQCI), and pilot testing the tool for feasibility and applicability in SNCUs.

Development of SQCI: A team consisting of six experts from national and state NIPI team developed a comprehensive tool drawing relevant indicators from SNCU online web portal. The process, spanning over a four month period, involved field visits and observations by pediatricians and statisticians. While defining the indices, due considerations were given on whether those were in accordance with global norms and standards for measuring quality of clinical care, user-friendliness, access to available data, ability to do self-assessment, and utility to Government for providing timely feedback. The focus was to have a dynamic model that could assess the optimal utilization of services, identify gaps in skills and clinical practices that influence the case fatality in every SNCU. For each of these objectives, most appropriate indicators were identified and put into a statistical model to arrive at a composite index. This was then piloted in one SNCU to test for its reliability, feasibility and usefulness in public health settings.

Initially, six indices were selected for SQCI, which also included an index on total deaths in the SNCU. Since this index was not able to measure the specific quality of care issues in the SNCU, it was replaced with mortality in normal weight babies (≥2500 gram). Additionally, one more indicator was added on inborn birth asphyxia index, to measure whether asphyxia was managed adequately in the labour room, and its subsequent load and implication on SNCUs in terms of bed occupation.

SQCI is a composite index of seven indices, each having a range from 0.01 to 1 (**Table I** and **Web Table I**): rational admission index, index for rational use of antibiotics, inborn birth asphyxia index, index for mortality in normal weight babies, low birth weight admission index, low birth weight survival index, optimal bed utilization index. Since the indices are comparing different items and each item has multiple properties, we have taken the geometric mean to calculate the final score. Based on the SQCI score, the performance of SNCUs was assessed as a Likert scale and labelled as good (SQCI 0.71- 1.0), satisfactory (SQCI 0.4- 0.7) and unsatisfactory (SQCI <0.4) [14].

Data collection: The SQCI tool was used in the states of Rajasthan and Odisha. All the parameters were retrieved in each quarter of the year, recorded in a predesigned excel database and SQCI score calculated by the program team. The indices were calculated for every month and then compiled for each quarter of the year. Each index was color coded (red for unsatisfactory, yellow for satisfactory and green for good) for better understanding. No additional data were collected for the purpose of the study.

Overall feedback, with particular emphasis on the two worst indicators, was provided to the districts. This facilitated improvement in the performance of the SNCUs.

Permission and approvals were obtained from concerned authorities (MoHFW, State governments) for retrieval and analysis of data from SNCU database. Anonymity and rights of patients and doctors were respected and therefore we did not consider individual level data in our analysis.

The data for SQCI computation was taken from an ongoing program and hence no ethical issues were involved. Since this was a program evaluation based on routinely collected data, no additional data was collected.

Data of five quarters starting from Jan- Mar 2016 to Jan- Mar 2017 were compared to assess the change in the quality of services. Paired *t* test was done to explore the statistical significance of the difference over a period of one year (from Jan-Mar, 2016 to Jan-Mar, 2017).

RESULTS

We present the results as composite scores aggregated from the SNCUs for the two states. In the pilot phase, data from 11 SNCUs out of total 92 SNCUs in the states of Rajasthan (n=59) and Odisha (n=33) were analyzed. The SQCI for Odisha increased from 0.44 to 0.57 over a period of one year while that of Rajasthan showed a marginal increase. (**Table II**, **Fig. 1**). Overall, the mean difference of the differences in the composite index of each unit between January to March, 2016 and same period in 2017 was 0.20 (95% CI 0.13- 0.28; P<0.001). Similar results were obtained for other indices. A significant improvement in the overall composite score was noted in Odisha [MD (95% CI) 0.22, (0.11-0.33) P=0.003] and Rajasthan [MD (95% CI) 0.17, (0.05-0.3) P=0.002] (data not shown).

We analyzed the key indices that are most amenable to improvement within the limited period of intervention. Those indices were index for rational use of antibiotics, index for mortality in normal weight babies and low birth

Table I Special Newborn Care Unit (SNCU) Quality of Care Index (SQCI) Calculations

Index	*Indicator*	*Numerator*	*Denominator*	*Formula for index*
Rational admission index	Proportion of newborns discharged within24 hours	No. of newborn discharged in <= 24 hours	Total number of newborn discharged	1 - (Number of newborn discharged in <= 24 hours/total number of newborn discharged)
Index for rational use of antibiotics	Proportion of newborns withsepsis received antibiotics	Number of newborns received antibiotics/diagnosed as sepsis	Total admissions	1 - [| (Total number of newborns received antibiotics -Number of newborns diagnosed as sepsis) | / total admission]
Inborn birth asphyxia index admissions)	Proportion of inborns admitted as birth asphyxia	Number of In-borns admitted to SNCU with birth asphyxia	Total number inborn admissions	1 - (Number of inborns admitted with birth asphyxia / total number inborn
Index for mortality in normal weight babies	Proportion of deaths in inborn infants weight 2500 g or more against totaladmissions of inborn infants weight 2500 g or more.	No. of deaths in inborn infants weight 2500 g or more	Total admissions of inborn infants weight 2500 g or more.	1 - (No. of deaths in inborn infants weight 2500 g or more/total admissions of inborn infants weight 2500 g or more)
Low birth weight admission Index	Proportion of low birthweight newborn babies (less than 1800) admitted to the unit	No. of newborn with birthweight less than 1800 g admitted	Total number of admissions	No. of newborn with birth weight less than 1800 g admitted/total number of admissions
Low birth weight survival index	Proportion of low birthweight babies (Between 1000 to1800 g) survived	No. of newborns with birthweight between 1000 to1800 g discharged alive	Total number of newborn with birth weight between 1000 to 1800 g admitted	No. of newborns with birth weight between 1000 to 1800 g discharged/total number of newborn with birthweight between 1000 to 1800g admitted in the same period.
Optimal bed utilisation index	Average number of newborns admitted per bed per month	Total admissions	Total number of beds × 6 × no. of months	1 - |(1 – average admission)? Average admission = (total admissions/total number of beds × 6 × no. of months) *Note:* 6 admissions per bed per month is considered as the desirable number. The proportion of average admission will mostly be in the range of 0 to 2.Where the proportion exceeds 2 then the default value will be 0.2.

The index and excel sheets have been designed to calculate the data on a periodic basis. If a longer duration (such as a quarter or half yearly is taken), then the proportions will vary. However, the calculation will not differ; The values of the indices will always be between 0.01 and 1; For Optimal bed utilisation index, we assume that 6 admissions per bed per month is a desired number; therefore, any value above or below 6 will be considered negative and calculated accordingly in the index. The denominator will include optimum number of neonates who can get admitted i.e Number of beds times 6 neonates per bed times number of months; Indices Rational Admission Index, Index for rational use of antibiotics, Inborn Birth Asphyxia Index and Index for Mortality in normal Weight babies are those indices where higher value reflects poor performance (for example, higher percentage of new borns discharged within 24 hours is undesirable). Therefore, to convert it into a positive value, the figure is subtracted from 1. Example: if 10% of all admissions are discharged in 24 hours, then it means that the value will be 1 – 0.1 = 0.9; Number of deaths in inborn infants with weight 2500 gram or more / total admissions of inborn infants weight 2500 gram or more" is multiplied by 9.99. Therefore 1 % death is equivalent to 9.99 points in the overall Index; In order to calculate a composite index, all the 7 indices are multiplied and then root of 7 of their product is calculated in order to get a geometric mean. The formula for calculating the composite index is shown below.

*SNCU Performance Index = 7∀ (Rational Admission Index X Index for rational use of antibiotics X Inborn Birth Asphyxia Index X Index for Mortality in normal Weight Babies X Low Birthweight Admission Index X Low Birthweight Survival Index X Optimal bed utilisation Index); * Ideal value for SQCI and all the 7 indices will be 1.*

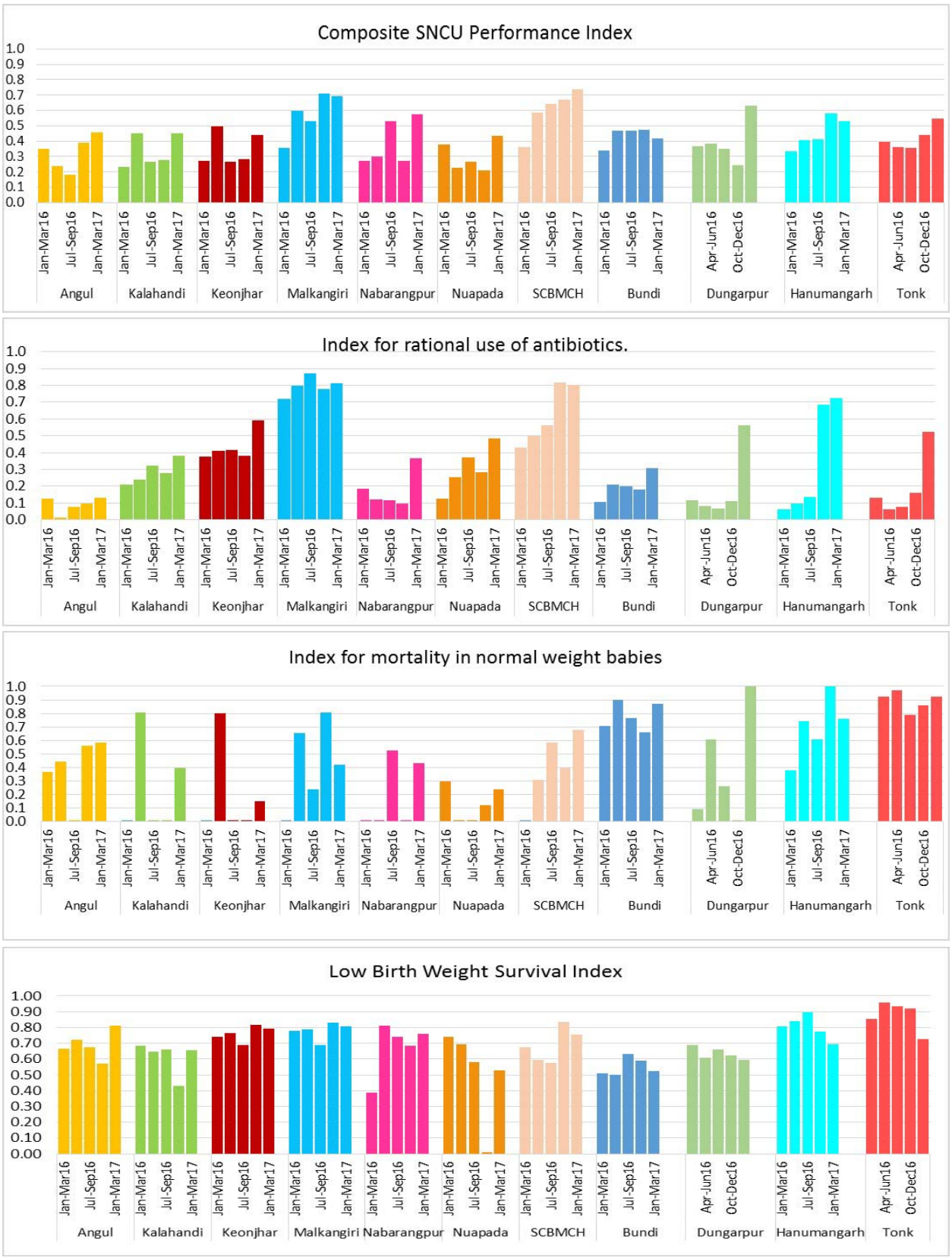


Fig. 1 Comparison of select indices of SQCI model across different SNCUs in selected districts of two states in India in 2016-2017.

Table II Indices to Measure Quality of Care in SNCUs in India Based on SQCI Model

Time period	*SQCI*	*Rational admission index*	*Index for rational use of antibiotics*	*Inborn birth asphyxia index*	*Index for mortality in normal weight babies*	*Low birth weight admission index*	*Low birth weight survival index*	*Optimal bed utilization index*
Odisha (7 SNCUs combined)								
I qtr 2016	0.44	0.91	0.34	0.70	0.40	0.27	0.66	0.20
II qtr 2016	0.28	0.95	0.01	0.64	0.44	0.26	0.71	0.28
III qtr 2016	0.46	0.95	0.41	0.62	0.17	0.33	0.65	0.47
IV qtr 2016	0.44	0.94	0.42	0.62	0.09	0.34	0.66	0.63
I qtr 2017	0.57	0.99	0.50	0.69	0.36	0.27	0.81	0.74
Rajasthan (4 SNCUs combined)								
I qtr 2016	0.50	0.74	0.55	0.79	0.71	0.19	0.67	0.27
II qtr 2016	0.40	0.76	0.11	0.90	0.87	0.18	0.71	0.20
III qtr 2016	0.40	0.73	0.12	0.89	0.69	0.19	0.76	0.20
IV qtr 2016	0.49	0.78	0.29	0.89	0.71	0.21	0.70	0.35
I qtr 2017	0.52	0.80	0.51	0.82	0.67	0.20	0.62	0.39
MD (95% CI) [a]	0.20 (0.13-0.28)[b]	0.07 (0.03-0.11)[b]	0.28 (0.16-0.41)[c]	-0.01 (-0.05-0.03)	-0.33 (-0.52,-0.14)[b]	0.008 (-0.02--0.03)	0.01 (-0.09-0.12)[b]	0.14 (0.007- 0.27)[b]

[a]*Mean difference in scores in each unit in first quarter of 2016 and 2017;* [b]*P<0.05;* [#]*P<0,001, SNCU: Special newborn care unit; SQCU: SNCU quality of care index;* [^]*I quarter: January-March, II quarter: April-June, III quarter: July-September, IV quarter: October-December.*

weight survival index. An analysis of every unit for the difference in these indices for the same time periods showed a significant improvement. A positive effect in terms of an improvement in the overall composite score was observed one year after the initiation of the QI model (data available at *https://sncuindiaonline.org*).

DISCUSSION

This study describes the development of a composite index and its application in two states of India. Our results showed SQCI in the SNCUs could be utilized for improving quality of services. An analysis of the SQCI over a period of one year showed a significant improvement in both the states.

Our findings demonstrate that program managers can use the tool to monitor the FBNC program. In the state of Rajasthan, the SQCI scores were utilized to initiate discussions on the challenges and discuss areas for improvement such as rational use of antibiotics, admission criteria and inpatient management of LBW newborns. Similarly, in Odisha, this model was used to identify and prioritize the shortfalls that were addressed during supportive supervision by the medical officers as part of the routine program.

Globally, it is now known that quality improvement (QI) models work in diverse cultures and locations [15]. Studies have shown that a regular system of QI intervention generally leads to improved adherence to health care delivery practices [8,12,13]. A QI project in six tertiary care hospitals in India, focused on interventions for increasing awareness on health care associated infections, improving compliance to infection control measures and monitoring rational antibiotic use reported. Periodic visits, rapid assessments and feedback, training and action at public health facilities has been reported to lead to improvement in adherence to QI guidelines in labor rooms in Rajasthan [8]. Periodic monitoring of labor rooms and newborn care facilities in Bihar also resulted in favorable outcomes [13,17]. Though on-site real time observations to assess quality of delivery of services have their own merits, yet it is a cost-and-resource intensive exercise and hence, may not be a preferred option for public health program [13].

Several QI models that have attempted to improve the quality of services have focused on babies with LBW [18-21]. The goals of these models were to identify and explain variations in clinical practices and patient outcomes from the routinely collected secondary data on newborns weighing less than 1500g [19]. Our assessment is based on the online database maintained by the health system, which is similar to those models. In our country, the purpose of setting up SNCUs was to take care of LBW babies primarily. However, reports suggest that the bulk

WHAT IS ALREADY KNOWN?

- There are multiple methods available to assess quality of services from routinely collected data.

WHAT THIS STUDY ADDS?

- It is possible to calculate indices (SQCI) based on available data that serve as proxy to quality of services.
- It is feasible to implement SQCI in public health settings for quality improvement.

of admissions to SNCUs are contributed by babies whose birthweights are more than 2500 [5,6]. Our approach therefore included babies of all birth weights.

An advantage of our approach is the ease with which data can be assembled and analyzed without relying on any special technical help. In our case, concurrently and routinely collected data from SNCUs were used which was independent of the process of medical records data abstraction. The indicators used to calculate SQCI are objective in nature, and less likely to be influenced by individual perceptions. Another advantage of our approach is that every SNCU in-charge in the country has access to review their own performance through the online portal, which is an advantage in terms of efficiency and feasibility.

Our limitations were that we captured only the providers' performance and users' perspectives were completely missed out. Although an important component in itself [22], we did not include them due to feasibility issues. Certain indices such as newborns discharged within 24 hour do not capture the reasons for admission, which is a drawback. Secondly, an independent evaluation to assess the validity of SQCI indices was not undertaken and it remains a limitation. In order to obtain some feedback on the reliability of SQCI, trained neonatologists did an independent assessment of select SNCUs, although this was not very objectively done. The overall feedback given by the experts confidentially corroborated well with the inferences drawn based on data driven QI model. Our experiences from 11 SNCUs across two states represent diverse locations lending to a possible generalizability with states with similar health indicators.

Government at both national and state levels were in support of QI initiatives using SQCI. Use of an existing mechanism of surveillance without any major external support for QI makes it more feasible as compared to the existing QI models. Implemented within the existing health systems, infrastructure and human resources, it contains a few components that can be easily added onto the existing system.

The SQCI index is a useful tool to evaluate the quality of neonatal care services in the Indian Special Newborn Care Units. The index can be used to follow a unit's performance over time or to benchmark various units and for quality improvement.

Contributors: HK: conceptualized SQCI and provided technical oversight of the process of SQCI analysis and use; RK: developed the statistical model during conceptualization of SQCI, analyzed data, interpreted the results and contributed to writing of the manuscript. VA,AK: provided technical support during conceptualization of SQCI, monitoring indicators and reviewed the manuscript; AAB: contributed in the framing of monitoring indicators and reviewed the manuscript SBN: reviewed the literature and drafted the manuscript; PC,PKS: implemented SQCI in their respective states, reviewed manuscript and provided inputs.

Funding: This study was conducted as part of the Newborn care project supported by Norway India Partnership Initiative (NIPI); *Competing interest*: None stated.

REFERENCES

1. Facility based newborn care: Operational guidelines. *In*: Ministry of Health and Family Welfare, editor. New Delhi: Ministry of Health and Family Welfare, Government of India; 2011.
2. Ministry of Health and Family Welfare. Health Management Information System. *In*: Ministry of Health and Family Welfare, editor. Ministry of Health and Family Welfare, Govt of India; 2017.
3. MOHFW. Special Newborn Care Units in India. *In*: Ministry of Health and Family Welfare, editor. New Delhi 2017.
4. Strengthening Facility Based Paediatric Care: Operational Guidelines for Planning & Implementation in District Hospitals. *In*: Child Health Division, Ministry of Health and Family Welfare, Government of India, New Delhi. September 2015. Accessed on November 16, 2020. Available from: *https://nhm.gov.in/images/pdf/ programmes/child-health/guidelines/Strenghtening_FacilityBasedPaediatricCare-OperationalGuidelines.pdf*
5. Neogi SB, Malhotra S, Zodpey S, Mohan P. Assessment of special care newborn units in India. Health Pop Nutr. 2011;29:500-9.
6. Neogi SB, Malhotra S, Zodpey S, Mohan P. Challenges in scaling up of special care newborn units-Lessons from India. Indian Pediatr. 2011;48:931-5.
7. Sharma G, Powell-Jackson T, Haldar K, Bradley J, Filippi

V. Quality of routine essential care during childbirth: Clinical observations of uncomplicated births in Uttar Pradesh, India. Bull World Health Organ. 2017;95:419-29.
8. Iyengar K, Jain M, Thomas S, et al. Adherence to evidence based care practices for childbirth before and after a quality improvement intervention in health facilities of Rajasthan, India. BMC Pregn Childbirth. 2014;14:270.
9. Chauhan M, Sharma J, Negandhi P, Reddy S, Sethy G, Neogi S. Assessment of newborn care corners in selected public health facilities in Bihar. Indian J Public Health. 2016;60:341-6.
10. Chawla D, Suresh GK. Quality improvement in neonatal care - A new paradigm for developing countries. Indian J Pediatr. 2014;81:1367-72.
11. Neogi SB, Malhotra S, Zodpey S, Mohan P. Does facility-based newborn care improve neonatal outcomes? A review of evidence. Indian Pediatrics. 2012;49:651-58.
12. Sarin E, Kole SK, Patel R, et al. Evaluation of a quality improvement intervention for obstetric and neonatal care in selected public health facilities across six states of India. BMC Pregn Childbirth. 2017;17:134.
13. Neogi SB, Shetty G, Ray S, Sadhukhan P, Reddy SS. Setting up a quality assurance model for newborn care to strengthen health system in Bihar, India. Indian Pediatr. 2014;51:136-8.
14. Vagias WM. Likert -type scale response anchors. Clemson University: Department of Parks, Recreation and Tourism Management, 2006.
15. Nadeem E, Olin SS, Hill LC, Hoagwood KE, Horwitz SM. Understanding the components of quality improvement collaboratives: a systematic literature review. Milbank Q. 2013;91:354-94.
16. Mehndiratta A. Quality Improvement of Facility Based New Born Care in India: ACCESS health International; 2014; Available from: *http://accessh.org/wp-content/uploads/2014/07/Quality-Improvement-of-Facility-Based-Newborn-Care-in-India-Poster.pdf*
17. Sharma J, Neogi S, Negandhi P, Chauhan M, Reddy S, Sethy G. Rollout of quality assurance interventions in labor room in two districts of Bihar, India. Indian J Public Hlth. 2016;60:323-8.
18. Horbar JD. The Vermont Oxford Network: Evidence-based quality improvement for neonatology. Pediatrics. 1999;103:350-9.
19. Horbar JD, Rogowski J, Plsek PE, et al. Collaborative quality improvement for neonatal intensive care. NIC/Q Project Investigators of the Vermont Oxford Network. Pediatrics. 2001;107:14-22.
20. Hernández-Borges AA, Pérez-Estévez E, Jiménez-Sosa A, et al. Set of quality indicators of pediatric intensive care in Spain: Delphi method selection. Pediatr Qual Safety. 2017;2:e009.
21. Profit J, Zupancic JA, Gould JB, et al. Correlation of neonatal intensive care unit performance across multiple measures of quality of care. JAMA Pediatr. 2013;167:47-54.
22. Lachman P, Jayadev A, Rahi M. The case for quality improvement in the neonatal intensive care unit. Early Human Dev. 2014;90:719-23.

CLIPPINGS

Recommendations for nutritional support for children during critical illness (*Intensive Care Med. 2020;46:411-425*)

The assessment of nutritional status is recommended in critically ill children at admission and throughout their PICU admission. It is recommended to perform anthropometric measurements on admission and regularly during admission.

Early commencement of enteral nutrition within 24 h of admission unless contraindicated, and increase enteral nutrition in a stepwise fashion until goal for delivery is achieved using a feeding protocol or guideline. Early enteral nutrition is recommended in term neonates and children who are stable on ECLS (extracorporeal life support), term neonates and children who are stable on pharmaceutical haemodynamic support.

In the acute phase, energy intake provided to critically ill children should not exceed resting energy expenditure, but after the acute phase, it should account for energy debt, physical activity, rehabilitation and growth. Minimum enteral protein intake of 1.5 g/kg/d to be given to avoid negative protein balance. In fluid-restricted critically ill children protein and energy dense formulations to be considered.

Surviving sepsis guidelines (2020) (Pediatric Critical Care Medicine, 2020 ;21:e52-e106)

This guideline has emphasized using serial trends instead of a single isolated value of lactate. It promotes use of restrictive fluid up to 40 mL/kg (previously up to 60 mL/kg) and each bolus of 10-20 mL/kg (previously 20 mL/kg) during resuscitation in settings where there is no support of ICU.

A time frame of 3 hour for initiation of antibiotics in children with sepsis but without shock has been set. Removal of intravenous line which is confirmed source of infection after establishing alternative access. Epinephrine or nor-epinephrine in place of dopamine as preferred inotrope.

CN RAGHUNATH
raghu.picu@gmail.com

Web Table I Overview of the Rationale of Indices Considered in the SQCI Model

Objectives of the SQCI model	*Index*	*Purpose of the index*	*Indicator obtained from the SNCU web portal*
To assess the optimal (& appropriate) utilization of services	Rational admission index	To know whether unnecessary admissions are being made (such as for healthy caesarean babies)	Proportion of new-born discharged within 24 hrs.
	Low birthweight admission index	To ascertain if the SNCU is fulfilling its envisaged role of addressing the vulnerable group of small (LBW or preterm babies <1800 g) babies	Proportion of low birth weight babies (<1800 g) admitted to the unit
	Optimal bed utilization index	To understand whether the newborn care units are over-crowded or underutilized	Average number of newborns admitted per bed per month
To identify gaps in skills and/or clinical practices	Inborn birth asphyxia index	To know about adequate management of third stage of labour and resuscitation services round the clock	Proportion of inborn admitted as birth asphyxia
	Rational use of antibiotics index	To know unnecessary antibiotic use of antibiotics as a difference between neonates received antibiotics and those with sepsis	Difference between neonates received antibiotics and those with sepsis as a proportion against the total admissions.
To track those survival/ mortality indexes that influence key outcome indicators (such as NMR; IMR)	Low birthweight survival index nance, feeding of preterm/LBW	To ascertain if clinical practices including temperature mainte-gms.) survived babies, KMC, supportive care and prevention of infection are being provided	Proportion of low birthweight babies (1000-1800 g)
	Mortality in normal weight babies	Normally there should not be any mortality in this. Mortality signifies critical congenital defect or nosocomial infection and lack of adherence to treat-ment guidelines.	Proportion of deaths that take place in in-born with birth weight 2500 g or more

RESEARCH PAPER

Tracking Weight-for-Age of Infants Using Home Based Newborn Care Plus by ASHA Workers

HARISH KUMAR,[1] RAJAT KHANNA,[2] VARUN ALWADHI,[3] ASHFAQ AHMED BHAT,[2] ANIL NAGENDRA,[2] PRASANT KUMAR SABOTH,[1] SUTAPA B NEOGI[4] AND AJAY KHERA[5]

From [1]VRIDDHI, IPE Global Ltd., New Delhi; [2]Norway India Partnership Initiative, New Delhi; [3]Department of Pediatrics, Kalawati Saran Children's Hospital, New Delhi; [4]International Institute of Health Management Research, New Delhi; and [5]Ministry of Health and Family Welfare, Government of India, New Delhi; India.

Correspondence to: Dr Ashfaq Ahmed Bhat, Norway India Partnership Initiative, New Delhi, India. bhatashfaq@gmail.com

Received: January 20, 2020; Initial review: February 19, 2020; Accepted: October 19, 2020.

Background: Malnutrition in all its forms remains a serious global concern, particularly affecting children, a highly vulnerable population group. Home visits during the first year of life using the community worker platform is an unexplored opportunity for making improvements in nutritional status.

Objective: To analyze the nutritional status (weight for age) of a cohort of infants between 3 and 12 months of age.

Design: Tracking weight for age of infants by ASHA workers.

Settings: 13 districts in the states of Bihar, Madhya Pradesh, Odisha and Rajasthan. **Intervention:** Home visits under a home-based newborn care program, home-based newborn care plus (HBNC+).

Methods: Norway India Partnership Initiative (NIPI) project supported implementation of HBNC+, in 13 districts across four states in India. A descriptive analysis of infants based on retrospective record based program data was done. The nutritional status (weight-for-age) of the cohort was analyzed. Categories were defined based on the *z*-scores of weight for age (≤-3 SD; ≤-2 SD and > -3 SD; and > -2 SD). Trend of malnutrition and proportions of children in each category at 3, 6, 9 and 12 months were assessed.

Results: At 3 months of age, out of 3,50,986 infants provided home visits, 1,82,049 (51.9%) were underweight as per WHO definition with weight for age *z*-score ≤– 2 SD; this reduced to 11.1% at 12 months of age. Difference of means at 3 months and 12 months significantly different for weight for age *z*-score (P<0.001). There was a decline in the proportion of children in severe and moderate malnutrition categories by 15% and 26%, respectively. **Conclusion:** Catch-up growth in terms of weight-for-age among malnourished children is possible within one year of age. Frequent contacts with the health care functionaries may result in this improvement, though it is difficult to conclude in the absence of an appropriate control.

Keywords: *Breastfeeding, Complementary feeding, Home visits, Underweight.*

Published online: *January 11, 2021;* ***PII:*** *S097475591600281*

More than 300,000 children die each year as a result of undernutrition before the age of five years [1,2]. Twelve of the 17 Sustainable Development Goals are relevant to nutrition [3]. Despite significant economic growth, one quarter of under-five children in India continue to suffer from malnutrition [4,5]. India has set a target of reducing stunting in under-five children by 40% [6]. Community-based approaches through counselling of mothers and family during home visitation have improved health outcomes [7,8]. However, most of the community level initiatives have focused on neonatal health outcome [9-17]. There is a dearth of evidence on the changes in the nutritional status of children till the age of 12 months.

Norway India Partnership Initiative (NIPI) project supported implementation of an innovation, Home Based Newborn Care Plus (HBNC+), an interpersonal counselling package bundling key child health and nutrition interventions for prevention of diarrhea, pneumonia and malnutrition through home visitation by the community health worker called accredited social health activist (ASHA). Under HBNC+, ASHA establishes the continuum of care by making four home visits at the age of 3, 6, 9 and 12 months. HBNC+ is designed to reduce child morbidity and mortality by accelerating delivery of essential evidence-based services; promotion of exclusive breastfeeding for 6 months and complementary feeding after 6 months, promotion of routine immunization, counselling for hand-washing, prophylactic distribution of oral rehydration solution (ORS) and iron-folic acid (IFA); and counselling on early child care and development (ECCD).

Editorial commentary: Pages 313-14

The objective of this longitudinal study was to analyze the nutritional status (weight for age) of a cohort of infants between the ages of 3 months and 12 months in 13 selected districts of four states in India.

METHODS

We analyzed record-based data from select districts in four states (Rajasthan, Odisha, Madhya Pradesh and Bihar). These were the districts earmarked for roll out of HBNC plus intervention by Norway India Partnership Initiative (NIPI) by the state Governments, and covered 70% of infant population of these states. The data pertains to infants who were born between 1 January, 2014 till 31 December, 2015, who were subsequently followed up in the community till December, 2016. The required data was derived from the records collected as part of the routine program of HBNC plus, wherein close to 2.5 million home visits were included.

Data on anthropometric measurement of children were routinely being recorded by anganwadi workers (AWW). As part of HBNC+, these data were collected by ASHAs and compiled in a pre-designed HBNC+ card with details of home visits provided under HBNC+. The HBNC+ cards were collected and compiled by ASHA supervisors during monthly ASHA meetings, who then populated these data into the HBNC+ registers to create a line list of infant beneficiaries. The line list from HBNC+ registers were digitally scanned by data entry operators (DEOs) during the monthly ASHA supervisors' meeting at the block level, who digitized the data and uploaded them on the Web Child health info at the district level, thereby creating an online line-list of infants covered through home visits under HBNC+. Infant-wise complete details of data recorded during HBNC+ home visits were extracted from this software for analysis. Care was taken to prevent data loss and minimize data entry errors during this process. Anthropometric data were transferred to WHO Anthro plus for calculation of *Z*-scores [18].

For the purpose of the study, the variables that could be objectively verified from records and families, such as date of birth, date of follow up visits, weight at 3, 6, 9, 12 months, availability of Mother and Child protection (MCP) cards, belonging to scheduled caste (SC) or scheduled tribe (ST), distribution of IFA syrup and ORS packets, and status (live/dead) at every visit were included. The primary outcome was weight-for-age (WFA) that was translated into *Z*-scores (WAZ). Infants were categorized into category 1 (WAZ ≤3 SD, severely underweight), category 2 (WAZ ≤-2 SD and above -3 SD); moderate underweight), and category 3 (WAZ >-2 SD).

Permissions were taken from the states and districts for accessing and analyzing data which were part of the ongoing health programs. Patient identifiers were removed in order to maintain anonymity.

Data analyses: Data were analyzed using SPSS version 24.0 and presented as means and standard deviations for continuous variables. The trend of WFA at 3, 6, 9, 12 months was analyzed. WAZ were compared by *t* test. Proportions of children in each category of nutrition at 3, 6, 9 and 12 months were described.

RESULTS

Data for 402986 infants were extracted and final analysis was done on 350986 infants (**Fig. 1**). The mean (SD) WFA at 3,6,9 and 12 months was 4.9 (0.8), 6.3 (0.9), 7.6 (1.0), and 8.8 (1.2) kg. At 3 months 62,513 (17.8%) infants had WAZ ≤-3 which was reduced to 9,368 (2.7%) at 12 months of age. At 3 months 1,19,536 (34.1%) infants had WAZ between -2 SD and -3 SD which was reduced to 29,593 (8.4%) at 12 months of age. Majority of infants (48.1% at 3 months and 88.9% at 12 months) had WAZ >-2 SD. The serial WFA for boys and girls across different categories of WAZ are also shown in **Table I**.

WAZ scores from 3 to 12 months in implementing districts were plotted against WHO growth standards (**Fig. 2**). At 3 months of age, the curve of reference population was positively skewed compared with the standard WHO curve. A shift to the right towards standard WHO curve was being seen between 6 and 9 months with the reference population curve being close to standard WHO curve at 12 months of age.

Clustering of weights plotted at different time-points was observed. Major clustering was reported at 4.5 and 5 kg at 3 months; at 6 and 6.5 kg at 6 months and at 7, 7.5 and 8 kg both at 9 months and 12 months.

Maximum improvement in WFA was reported in the districts with higher scheduled caste and scheduled tribe population **(Supp. Table I)**.

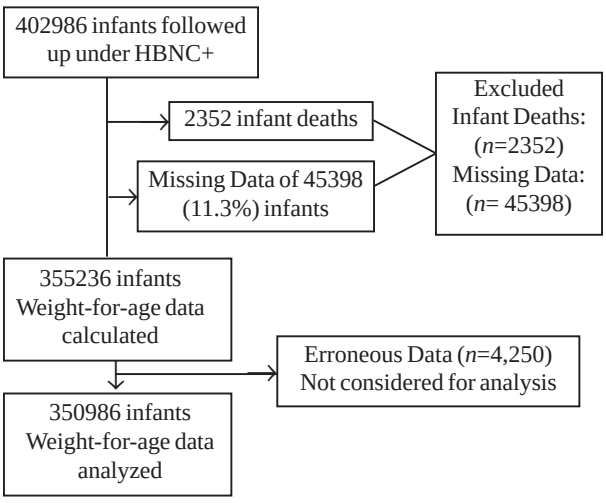


Fig. 1 Flow of participants in the study.

Table I Weight-for-age by Serial Assessments in Different Categories of Malnutrition (*N*=3,50,986)

Time	*WAZ <-3*	*WAZ -3 to -2*	*WAZ >-2*	*Mean diff.* (95% CI)[a]
At 3 mo				
Total	3.81 (0.01)	4.55 (0.01)	5.45 (0.01)	1.64
Boys	3.94 (0.01)	4.78 (0.01)	5.69 (0.01)	(1.63-1.64)
Girls	3.43 (0.01)	4.27 (0.01)	5.27 (0.01)	
At 6 mo				
Total	5.62 (0.01)	6.12 (0.01)	6.75 (0.01)	1.13
Boys	5.73 (0.01)	6.31 (0.01)	6.97 (0.01)	(1.12- 1.15)
Girls	5.29 (0.01)	5.90 (0.01)	6.60 (0.01)	
At 9 mo				
Total	7.13 (0.01)	7.46 (0.01)	7.88 (0.01)	0.74
Boys	7.23 (0.01)	7.62 (0.01)	8.06 (0.01)	(0.73 - 0.76)
Girls	6.84 (0.01)	7.27 (0.01)	7.75 (0.01)	
At 12 mo				
Total	8.59 (0.01)	8.77 (0.01)	8.99 (0.01)	0.40
Boys	8.68 (0.01)	8.90 (0.01)	9.14 (0.01)	(0.38 - 0.49)
Girls	8.36 (0.01)	8.61 (0.01)	8.89 (0.01)	

Data expressed as mean (SD) in kg; WAZ Weight-for-age z-score; [a]*between WAZ <-3 and WAZ >-2*

DISCUSSION

This study showed decline in the proportion of children with severe and moderate malnutrition by 15% and 26%, respectively at 12 months in HBNC+ implementation districts. The shift towards WHO reference curve observed over time was encouraging, showing that catch-up growth was possible.

This improvement may not be attributed to the intervention *per se* in the absence of any population-based control. Also, stunting (height for age) and wasting (weight for height) were not assessed due to paucity of data. The study did not capture data of children who were lost to follow-up or whose data were missing or erroneous. This may have led to biased estimates. However, ASHAs were provided guidance during regular supportive supervision visits conducted by their supervisors under HBNC+ to minimize data loss. The clustering of in weight was due to weight rounding off by AWW or ANM up to one decimal while recording them on the MCP card. This however, did not influence the analysis.

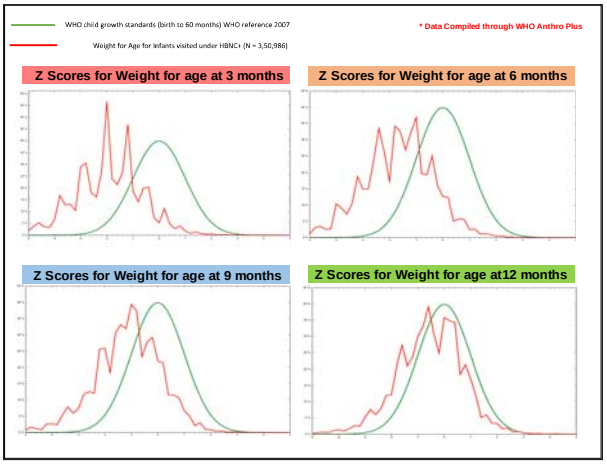


Fig. 2 Weight-for-age of reference population plotted on WHO child growth standards.

The concept of home visits during infancy is drawn from its success during the neonatal period. Frequent contact with the frontline workers, reinforcement of messages, and timely intervention such as home based treatment or referral in case of any illness result in favorable outcomes. There are limited evidences that home visits beyond neonatal period improve clinical and nutritional outcomes. Improvement in nutrition status with frequent home visits has been reported from Bangladesh [19]. Home visits were demonstrated to be a good strategy to promote healthy behaviors among children [20]. Improvement in the quality of food consumption was observed in a community based nutritional intervention program [21]. Significant differences between HBNC+ and non HBNC+ were seen for key child health outcomes such as exclusive breastfeeding, complementary feeding and IFA consumption in Rajasthan [22].

A significant proportion of LBW babies achieved complete catch-up in height by adulthood. However, their body mass index remained lower than those with normal birth weight babies [23]. Babies born as SGA showed good catch-up in weight and height in early childhood [24,25]; however, with significant difference in catch-up in weight than AGA babies till 1.5 years of age [25]. This is in contrast to our finding where catch-up growth (for weight) occurred within one year of age. However, the proportion of SGA or LBW was uncertain as records were only available from the age of three months.

To conclude, a review of records of weight-tracking of more than three lakh infants showed that catch-up growth in terms of weight was possible among malnourished children within first year of age. Frequent contacts with the health care functionaries may contribute to this improvement, though it is difficult to reach a definitive conclusion in the absence of an appropriate control.

***Acknowledgements*:** Child Health Division in Ministry of Health and Family Welfare, Government of India; State and District Health Society of Bihar, Madhya Pradesh, Odisha and Rajasthan for their support to implement HBNC+ innovation in 13 districts. *Contributions*: HK: conceptualized and provided overall guidance in the drafting of the manuscript; RK: compiled and analyzed data and drafted the manuscript; VA, AK: provided technical inputs in the drafting and finalization of the manuscript; AAB: guided the

data compilation, supervised the study and reviewed the manuscript; AN, PKS: supported the field implementation of HBNC+ and provided inputs in the manuscript; SBN: reviewed literature and supported the drafting of the manuscript. All the authors have approved the final version of the manuscript.

Funding: This study was conducted as part of the Newborn care project supported by Norway India Partnership Initiative (NIPI).
Competing interests: None stated.

REFERENCES

1. Black RE, Allen LH, Bhutta ZA, et al. for the Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: Global and regional exposures and health consequences. Lancet. 2008;371:243-60.
2. Walker SP, Wachs TD, Gardner JM, et al; International Child Development Steering Group. Child development: Risk factors for adverse outcomes in developing countries. Lancet. 2007;369:145-57.
3. Nutrition and the Post-2015 Sustainable Development Goals, A Technical Note. United Nations Systems Standing Committee on Nutrition. October, 2014. Accessed on November 10, 2019. Available from: *https://www.unscn.org/files/Publications/Briefs_on_Nutrition/Final_Nutrition%20and_the_SDGs.pdf*
4. National Family Health Survey (NFHS-3) 2005-2006. International Institute for Population Sciences. May 2008. Accessed on November 15, 2019. Available from: *http://rchiips. org/nfhs/nfhs3_national_report.shtml*
5. National Family Health Survey (NFHS-4) 2015-2016. International Institute for Population Sciences. December 2017. Accessed on November 15, 2019. Available from: *http://rchiips. org/nfhs/NFHS-4Reports/India.pdf*
6. Ministry of Health and Family Welfare, Government of India. National Health Policy 2017. Accessed on November 20, 2019. Available from: *https://www.nhp.gov.in/nhpfiles/national _health_ policy_2017.pdf*
7. Sinha LN, Kaur P, Gupta R, Dalpath S, Goyal V, Murhekar M. Newborn care practices and home-based postnatal newborn care programme Mewat, Haryana, India. Western Pac Surveill Response J. 2014;5.
8. BRAC. Scaling up and sustaining support for improved infant and young child feeding: BRAC's experience through the Alive & Thrive Initiative in Bangladesh. Dhaka, Bangladesh: BRAC, 2014. Accessed on November 30, 2019. Available from: *https://www.aliveandthrive.org/wp-content/uploads/2018/07/BRAC-Final-report-8.28.2014.pdf*
9. Tripathi A, Kabra S K, Sachdev HPS, Lodha R. Home visits by community health workers to improve identification of serious illness and care seeking in newborns and young infants from low- and middle-income countries. J Perinatol. 2016;36:S74-82.
10. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L. Evidence-based, cost-effective interventions: How many newborn babies can we save? Lancet. 2005;365:977-88.
11 Bhutta ZA, Memon ZA, Soofi S, Salat MS, Cousens S, Martines J. Implementing community-based perinatal care: results from a pilot study in rural Pakistan. Bull World Health Organ. 2008;86:452-59.
12. Baqui AH, El-Arifeen S, Darmstadt GL, *et al*. Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: A cluster-randomized controlled trial. Lancet. 2008;371:1936-44.
13. Gilmore B, McAuliffe E. Effectiveness of community health workers delivering preventive interventions for maternal and child health in low- and middle-income countries: a systematic review. BMC Public Health: 2013;13: 847.
14. Gogia S, Sachdev HPS. Home visits by community health workers to prevent neonatal deaths in developing countries: A systematic review. Bull World Health Organ. 2010;88:658-666B.
15. Aboubaker S, Qazi S, Wolfheim C, Oyegoke A, Bahl R. Community health workers: A crucial role in newborn health care and survival. J Global Health.2014; 4:020302.
16. George A, Menotti EP, Rivera D, Montes I, Reyes CM, Marsh DR. Community case management of childhood illness in Nicaragua: Transforming health systems in underserved rural areas. J Health Care Poor Underserved; 2009;20:99-115.
17. Yeboah–Antwi K, Pilingana P, Macleod WB, et al. Community case management of fever due to malaria and pneumonia in children under five in Zambia: A cluster randomized controlled trial. PLoS Med. 2010;7:e1000340.
18. WHO AnthroPlus for Personal Computers: Software for assessing growth of the world's children and adolescents. Department of Nutrition for Health and Development. World Health Organization. 2009.
19. Menon P, Nguyen PH, Saha KK, et al. Combining intensive counseling by frontline workers with a nationwide mass media campaign has large differential impacts on complementary feeding practices but not on child growth: Results of a cluster-randomized program evaluation in Bangladesh. J Nutr.2016;146:2075-84.
20. Nti CA, Lartey A. Influence of care practices on nutritional status of Ghanaian children. Nutr Res Pract. 2008;2:93-99.
21. Pavithra G, Kumar S G, Roy G. Effectiveness of a community-based intervention on nutrition education of mothers of malnourished children in a rural coastal area of South India. Indian J Public Health. 2019;63:4-9.
22. Yonzon KK, Dehingia N, Alwadhi V, et al. An Assessment of home-based newborn care plus innovation in six districts of Rajasthan: A cross sectional comparative analysis. Indian J Comm Health. 2019;31:338-46.
23. Brandt I, Sticker EJ, Gausche R, Lentze MJ. Catch-up growth of supine length/height of very low birth weight, small for gestational age preterm infants to adulthood. J Pediatr. 2005;147:662-8.
24. Itabashi K, Mishina J, Tada H, Sakurai M, Nanri Y, Hirohata Y. Longitudinal follow-up of height up to five years of age in infants born preterm small for gestational age; comparison to full-term small for gestational age infants. Early Hum Dev. 2007;83:327-33.
25. Shoji H, Watanabe A, Awaji A, *et al*. Intrauterine growth restriction affects z-scores of anthropometric parameters during the first 6 years in very low-birth-weight-children born at less than 30 weeks of gestation. J Dev Orig Health Dis. 2019:1-5.

Supplementary Table I Proportion of Infants With WAZ ≥2 in Districts With Predominant Scheduled Caste (SC) and Scheduled Tribe (ST) Population

Age	*Districts with*		
	Predominant SC population	*Predominant ST population*	*Predominant SC and ST population*
3 mo	46%	47%	49%
6 mo	59%	61%	62%
9 mo	77%	77%	79%
12 mo	89%	88%	89%

RESEARCH PAPER

An Assessment of Implementation of Family Participatory Care in Special Newborn Care Units in Three States of India

HARISH KUMAR,[1] ASHFAQ BHAT,[1] VARUN ALWADHI,[2] ARTI MARIA,[3] RAJAT KHANNA,[1] SUTAPA B NEOGI[4] AND AJAY KHERA[5]

From [1]Norway India Partnership Initiative; [2]Departments of Pediatric, Kalawati Saran Children Hospital; [3]Department of Pediatrics, Ram Manohar Lohia Hospital; [4]Indian Institute of Public Health; and [5]Child Health Division, Ministry of Health and Family Welfare, Government of India; New Delhi, India.

Correspondence to: Dr Harish Kumar, Former Director, Norway-India Partnership Initiative, New Delhi, India. harishalwadhi@hotmail.com

Received: December 17, 2018; Initial review: May 20, 2019; Accepted: November 09, 2019.

Objective: To study special newborn care units (SNCUs) in terms of family participatory care (FPC) quality initiative as per Government of India guidelines in select public health facilities, and to document the perspectives of the doctors and mothers.

Design: Cross-sectional.

Settings: SNCUs with functional FPC units in the states of Odisha, Madhya Pradesh and Rajasthan.

Participants: 38 SNCUs; doctors and nurses in-charge of the unit; and two eligible mothers per unit, one inside the step-down unit and second outside the step-down unit whose newborns were admitted to special new-born care unit, having a stable baby weighing above 1500 g.

Intervention: The states implemented FPC as per Government of India guidelines using National Health Mission funds across special newborn care units. This assessment involved onsite observation and interviews of key providers.

Outcome: Proportion of facilities providing regular counselling sessions, enabling support to mothers, recording FPC information; perspectives of health providers on improvement of breastfeeding and kangaroo mother care; proportion of eligible mothers practicing FPC, exclusively breastfeeding, and providing kangaroo mother care services.

Results: Out of 38 SNCUs, we found that FPC sessions for mothers were happening in 36 (95%) facilities. SNCUs provided enabling support to mothers on FPC (74.2%), held regular sessions for the families (70.6%), nurses assisted mothers and family members for breastfeeding and kangaroo mother care (76.4%) and FPC information were recorded (70.6%).

Conclusions: The assessment of facilities where FPC was implemented showed that SNCUs were equipped to implement FPC in public health settings.

Keywords: *Breastfeeding, Family centered care, Kangaroo mother care, Low birthweight neonates, Quality improvement.*

***Published online:** January 02, 2021**; PII:** S097475591600270*

Family-centered care (FCC) is an approach to the planning, delivery and evaluation of services engaging providers, patients and families [1]. A recent Cochrane review iterated the positive effect that FCC has on the adequacy of children's care, parental satisfaction, and costs [2]. FCC in newborns has been known to reduce duration of hospital stay, improve wellbeing of preterm babies, improve breastfeeding rates, have better allocation of resources, and increase parent-infant bonding [3]. The outcome in very low birthweight infants without severe perinatal diseases have resulted in better short term gains like full enteral feeding, early hospital discharge, better neurobehavioral performance and weight-gain [4]. In another study, it was found that in-hospital developmental care led to less morbidities and better clinical outcomes [5].

Preliminary results from tertiary care centers in India have shown that it is feasible to adopt FCC in a developing country setting [3]. However, it has been suggested that implementation in public health settings would require exploration [6]. The barriers on health system factors to its effective implementation need to be identified [7]. In India, facility-based newborn care has grown rapidly in the recent past. It is also reported that around 10% of babies treated in special newborn care units (SNCUs) do not survive till the age of one year after discharge [8]. Findings from these observations call for a strategy to ensure continuity of services beyond their hospital stay. To address this gap, Government of India adapted FCC in the Indian context as family participatory care (FPC) focusing on babies weighing more than 1500 g who do not require oxygen and IV fluids [9].

Editorial commentary: Pages 313-14

The objective of the current study was to assess the FPC quality initiative of SNCU in these public health

facilities. The specific objectives included assessment with regards to providing regular counselling and enabling support to mothers on implementation of FPC and mechanism of reporting within the health system. We also explored the perspectives of doctors on the outcome of FPC implementation such as improvement of breastfeeding and kangaroo mother care (KMC).

METHODS

The assessment was conducted between January, 2018 and March, 2018 across three states (Odisha, Madhya Pradesh and Rajasthan) in public health facilities, where FPC was implemented. The districts that had completed the trainings of doctors and nurses were recognized as districts that were implementing FPC [10]. Till December 2017, a total of 69 districts started implementing FPC. However, 50 districts had started reporting their data on a monthly basis. It was felt necessary that a rapid assessment would help identify the gaps in implementation.

For the purpose of the current assessment, 38 of the 50 facilities were selected through purposive sampling based on geographical location and duration of implementation of FPC (8 from Madhya Pradesh, 10 from Odisha and 20 from Rajasthan).

The study sample included SNCUs with functional FPC units, doctors and nurses in-charge of the unit, and two eligible beneficiaries (preferably mothers, one inside the SNCU step-down unit and second outside the SNCU with newborn admitted in the SNCU) who provide FPC to a stable baby weighing above 1500 g. Data were collected by one assessor in each of the SNCUs, who had prior knowledge about health systems and were trained in conducting field level assessments. They were trained by the research team before collection of data. The data comprised of three components based on observations and interviews on the day of the visit:

Facility assessment: This was done mainly on the basis of observations as per a predefined simple checklist and record reviews supplemented by interviews, wherever required. Based on the observations, every parameter in the checklist was assigned a score. The scores varied between 0 (worst) and 4 (best). The scores were then converted into percentages (0=<10%, 1=10-40%, 2=40-60%, 3=60-80%, 4=>80%). The parameters included: Mothers received enabling support from nurses on FPC through observations (assessed on the basis of availability of supplies, chairs for family members in step down units, availability of training space and audio visual equipment, each having a score of 1); Regular training sessions held for the families on FPC through observations and interview with families (Always=4, Occasionally missed=3, Sometimes held=2, Occasionally held with Audio visual aids=1, never=0); Mothers and family members assisted by nurses for breastfeeding and Kangaroo mother care (KMC) through observations and interview with families (Always=4, Occasionally=3, Sometimes=2, Occasionally held, only if mother asks=1, never=0); FPC information recorded regularly through review of SNCU and FPC records and registers (Register records details of every mother=4, Mostly recorded but not complete=3, Provision in register but occasional information=2, Provisional but no information=1, No provision in register=0). The facilities were assessed based on the scores calculated from the observations.

Health worker perspective: Doctors and nurses in-charge of the unit (1 per SNCU) were interviewed to assess their perspectives about the possible outcomes of FPC implementation like breastfeeding rates, quality of care, KMC, hospital acquired infections. Their views on improvement of FPC were sought. These were elicited by administering a semi-structured tool designed for this assessment.

Maternal practices: Mothers were asked about their practices with regards to breastfeeding, KMC, and trainings received after their babies were admitted to SNCUs. Any problems faced by the mothers with regards to FPC were explored. A semi-structured tool was used for this purpose. The perspectives of doctors and nurses and practices of mothers were expressed as proportions. Challenges of implementing FPC and ways to overcome them were also noted.

Permission was taken from the state and district authorities before start of the data collection. Since the assessment was a part of the ongoing national program, no approval from any ethics committee was taken. However, verbal consent was obtained from every respondent who participated in the study.

RESULTS

Out of 38 SNCUs assessed, we found that FPC sessions for mothers were being conducted in 36 (95%) facilities. These were found either by direct observation or were extracted from the FPC records maintained by the units. A total of 68 doctors (49.2% of doctors posted) and 253 nurses (54.3% of nurses posted) were trained on FPC.

Every unit had a dedicated training space while 36 (95%) of them had facilities like audio visual equipment and other facilities for conducting trainings. However, only 16 SNCUs had training session plans displayed in the training area.

137 (72%) out of 190 eligible women/family members were observed providing FPC inside the SNCU. On an average, five FPC-eligible mothers were found inside each SNCU and four of them were found to provide FPC routinely. In 36 facilities (95%), mothers were provided with supplies like gowns, slippers, nail cutter, soap but chairs were available for family members in step down unit in only 84% (32) facilities. Although the performance of the units varied for the parameters such as providing enabling support from nurses on FPC for mothers, holding regular training sessions for the families, nurses assisted mothers and family members for breastfeeding and KMC, and recoding of FPC information. Only 13 (34%) fulfilled all the essential criteria (score of 100%). The average scores for some key parameters are summarized in **Table I**.

Majority of the respondents (37, 97%) expressed that the quality of care had improved since the time of implementation of FPC. All of them concurred that breastfeeding and KMC practices had improved with its implementation. Follow-up rates of newborns after discharge from SNCUs also improved. The staff expressed that it was difficult to maintain the supplies and logistics. With multiple people entering the unit for various tasks such as KMC and institutional follow up, the FPC sessions got affected. The internal partitions were not enough to prevent distractions.

The mean gestational age of babies who were beneficiaries of FPC was 34.4 provide SD weeks. Of all the participants, 56 (74.6%) weighed less than or equal to 2 kg and all of them were born preterm. Most (73, 97.3%) of the respondents interviewed mentioned that they had received FPC sessions; although, some of them expressed that they could not follow the sessions due to language problem. Once they entered the SNCU, they sometimes found it difficult to adhere to the instructions. For instance, some cultural practices prevented them from following all aseptic precautions like removal of rings and bangles. On an average, mothers stayed for 3.4 SD hours inside the SNCU; 33 (47.1%) of them stayed for at least 3 hours while 14 (20%) stayed for at least 5 hours. Among those whose baby's weight was less than or equal to 2 kg, mothers spent 4.2 (SD) hours inside SNCUs. Out of them, 49 (87.5%) reported to have practiced KMC for 1.7 hours on one occasion (**Table II**). Number of such occasions varied from 3-6 times a day.

Table I Average Scores of Facility-Based Assessment for Family Participatory Care in Three States of India

Parameter assessed	*Average score*[a]
Mothers received enabling support from nurses on FPC	74.2%
Regular training sessions held for the families on FPC	70.6%
Mothers and family members assisted by nurses for breastfeeding and KMC	76.4%
FPC information recorded regularly	70.6%

[a]*Score varied from 0 (worst) to 4 (best). Scores were converted to percentages (0=<10%, 1=10-40%, 2=40-60%, 3=60-80%, 4=>80%); FPC: family participatory care; KMC: Kangroo mother care.*

DISCUSSION

The assessment of facilities where FPC was implemented showed that SNCUs were equipped to implement FPC in public health settings. Majority of the mothers were practising FPC, exclusively breastfeeding and providing KMC.

The study findings have to be interpreted cautiously in the light of the methodology used. This was a rapid assessment conducted in select public health facilities to gain an insight into the implementation of the guidelines. The perspectives of the implementing team (doctors and nurses) were explored that might have introduced some amount of subjectivity, since these were not correlated from available records. Separate interviews with nurses could have yielded more information. However, the purpose was not to identify faults but to capture their perceptions and bottlenecks for appropriate remedial measures. Owing to limited time and resources, the assessment was based on observations of a single day and that too, on a convenience sample of mothers, which could have influenced the results. FPC is being implemented and scaled up as a national program. In the absence of any comparator it was not possible to evaluate the impact of FPC. Pre- and post- intervention study was

Table II Practices of Beneficiaries on Family Participatory Care Implementation

Parameter assessed	*Response*
Gestational age of babies, wk (n=72)[a]	34.4 (3.3)
Respondents allowed to participate in care of the child inside SNCU	70 (93.3)
Stay with the baby inside SNCU, h (n=67)[a]	3.4 (0.3)
Respondents who received any FPC session	73 (97.3)
Mothers practicing exclusive breastfeeding or exclusively giving expressed breast milk	70 (93.3)
Mothers who knew that exclusive breastfeeding should be done for 6 mo	67 (89.0)
Respondents who practiced KMC for babies <2 kg (n=59)	55 (93.2)
Duration of KMC (n=57)[a]	1.6 (0.13)
Respondents who felt that mothers should be allowed to enter SNCUs	74 (98.6)

All values in n (%) or [a]mean (SD); FPC: family participatory care; KMC: kangroo mother care; SNCU-special newborn care unit.

WHAT IS ALREADY KNOWN?

- Family participatory care (FPC) is effective for improving care of newborn admitted to neonatal units.
- It improves breastfeeding, and reduces duration of stay in hospitals and maternal anxiety.

WHAT THIS STUDY ADDS?

- It is feasible to implement FPC as Special Newborn Care Unit quality improvement initiative in health systems settings.
- FPC is easy to initiate but needs strong health systems support for optimal results.

not possible because there were no documented records of the practices like breastfeeding and KMC before FPC was rolled out.

In the only study conducted in a tertiary-care hospital in India, the average gestational age was 36.4 weeks, and majority of the babies were full term (>75%), with an average weight of more than 2300 g. Around one-fourth of them required intravenous lines [3]. On the other hand, the FPC quality initiative in India at district level focuses on babies more than 1500 g not requiring oxygen and intravenous (IV) fluids. In this assessment, only 18 (24%) of the babies had weight less than or equal to 1500 g who did not require oxygen or IV fluids but received FPC. Absence of oxygen or IV fluids, irrespective of weight and gestational age, appears to be a more practical approach to identify eligible FPC participants in health systems settings.

One of the benefits of FPC noticed in the study was improved implementation of KMC. Reports from India have reported duration of KMC per day to be 3-5 hours in NICUs [12-14]. Interventions such as presence of physician champions and quality improvement projects have increased the duration of KMC to 6 hours or more per day [13,14]. In our assessment, it was 1.7 hours on one occasion that would translate to more than 6 hours a day if repeated 3-6 times. There is ample scope to strengthen it further. Reports suggest that breastfeeding rates decline after admission to newborn units [15-17]. In this assessment, 93.3% of newborns were given breast milk which suggests that FPC might promote the breast-feeding practices as per the national guidelines [18].

FPC has now been accepted in most of the facilities as per the national guidelines. However, three inputs are suggested for further strengthening of FPC implementation in SNCU units: supportive supervision for FPC should be an integral component of overall supportive supervision in newborn facilities; infrastructure should be strengthened to provide more amenities to mothers; more focus should be given on increasing the duration of FPC. Multiple innovative ways can be explored for increasing duration of FPC by mothers.

To summarize, FPC needs to be rolled out within health systems along with strengthening of health infrastructure and service delivery. However, more robust research is needed to understand the impact of FPC on clinical and developmental outcomes within public health settings.

Contributors: HK,AB: conceptualized the study design and methods and provided inputs on the manuscript; VA, AM: provided inputs during the execution of the study and provided critical inputs on the manuscript; RK: supervised the data collection process, performed analysis and interpreted results and provided inputs in the manuscript; SBN: reviewed the literature and drafted the manuscript; AK: facilitated in the study in the health system settings and provided inputs on the manuscript; All the authors reviewed and approved the final draft.
Funding: National Health Mission, Government of India; *Competing Interest*: None stated.

REFERENCES

1. Feeg VD, Paraszczuk AM, Cavusoglu H, Shields L, Pars H, Al Mamun A. How is family centered care perceived by healthcare providers from different countries? An international comparison study. J Pediatr Nurs. 2016; 31:267-76.
2. Shields L, Zhou H, Pratt J, Taylor M, Hunter J, Pascoe E. Family-centred care for hospitalised children aged 0-12 years. Cochrane Database Syst Rev. 2012;10:CD004811.
3. Verma A, Maria A, Pandey RM, Hans C, Verma A, Sherwani F. Family-centered care to complement care of sick newborns: A randomized controlled trial. Indian Pediatr. 2017;54:455-9.
4. Yu YT, Hsieh WS, Hsu CH, et al. Family-centered care improved neonatal medical and neurobehavioral outcomes in preterm infants: Randomized controlled trial. Phys Ther. 2017;97:1158-68.
5. Chen LC, Wu YC, Hsieh WS, et al. The effect of in-hospital developmental care on neonatal morbidity, growth and development of preterm Taiwanese infants: A randomized controlled trial. Early Hum Dev. 2013;89:301-6.
6. Kuo DZ, Houtrow AJ, Arango P, Kuhlthau KA, Simmons

JM, Neff JM. Family-centered care: Current applications and future directions in pediatric health care. Matern Child Health J. 2012;16:297-305.
7. Vázquez SA, Sellán SMC, Díaz MML. Family-centered care: A philosophy to be developed. Pediatr Neonatal Nurs Open J. 2017;5:1-5.
8. Neogi SB, Khanna R, Chauhan M, et al. Inpatient care of small and sick newborns in healthcare facilities. J Perinatol. 2016;36:S18-S23.
9. Ministry of Health and Family Welfre, Government of India. Family Participatory Care for Improving Newborn Health: Operational Guidelines for Planning and Implementation. Government of India: 2017.
10. Norway India Partnership Initiative (NIPI). Report on Scale up of FPC in the states of Odisha, Rajasthan, Madhya Pradesh. 2017. Accessed 31 March, 2018. *www.nipi.org.in*
11. Heidarzadeh M, Hosseini MB, Ershadmanesh M, Gholamitabar Tabari M, Khazaee S. The effect of kangaroo mother care (KMC) on breast feeding at the time of NICU discharge. Iran Red Crescent Med J. 2013;15:302-6.
12. Jayaraman D, Mukhopadhyay K, Bhalla AK, Dhaliwal LK. Randomized controlled trial on effect of intermittent early versus late kangaroo mother care on human milk feeding in low-birth-weight neonates. J Human Lactation. 2017;33: 533-9.
13. Soni A, Amin A, Patel DV, et al. The presence of physician champions improved kangaroo mother care in rural western India. Acta Paediatrica. 2016;105:e390-e5.
14. Joshi M, Sahoo T, Thukral A, Joshi P, Sethi A, Agarwal R. Improving duration of kangaroo mother care in a tertiary-care neonatal unit : A quality improvement initiative. Indian Pediatr. 2018;55:744-7.
15. Kair LR, Colaizy TT. Breastfeeding continuation among late preterm infants: barriers, facilitators, and any association with nicu admission? Hospital Pediatrics. 2016;6:261-8.
16. Rodrigues C, Teixeira R, Fonseca MJ, et al. Prevalence and duration of breast milk feeding in very preterm infants: A 3 year follow up study and a systematic literature review. Paediatr Perinat Epidemiol. 2018;32:237-46.
17. Hunter C, Gottheil S. Breastfeeding promotion: the NICU perspective. 2012. University of Western Ontario Medical Journal. 2012;81:31-2.
18. Tiwari S, Bharadva K, Yadav B, et al. Infant and Young Child Feeding Guidelines, 2016. Indian Pediatr. 2016;53:703-13.

RESEARCH PAPER

Special Newborn Care Plus Project in India: Preliminary Findings from Community-Based Follow-up of Newborns Discharged from Facilities

HARISH KUMAR,[1] ASHFAQ AHMED BHAT,[2] VARUN ALWADHI,[3] RAJAT KHANNA,[2] SUTAPA B NEOGI,[4] PRADEEP CHOUDHRY[2] AND PK PRABHAKAR[5]

From [1]VRIDDHI, IPE Global Ltd., [2]Norway India Partnership Initiative; [3]Department of Pediatrics, Kalawati Saran Children Hospital; [4]Indian Institute of Public Health Delhi; and [5]Ministry of Health and Family Welfare, Government of India; New Delhi, India.

Correspondence to: Dr Ashfaq Ahmed Bhat, Norway India Partnership Initiative, New Delhi, India. bhatashfaq@gmail.com

Received: April 10, 2019; Initial review: August 13, 2019; Accepted: December 11, 2019.

Objective: An innovation of structured community based followup of SNCU discharged babies by ANM and ASHA was piloted under Norway India Partnership initiative. The current study describes the survival status and other outcomes among newborns discharged from SNCUs and followed at community level in first 42 days of life.

Methods: It is a retrospective cohort study on newborns discharged from SNCUs from 13 districts across four states of India. Routine health systems data have been utilized to record key parameters like birth weight, sex, weights during follow-ups, any illnesses reported, status of feeding and survival status. These were compared between normal and low birth weight babies. Newborns discharged from special newborn care units (SNCUs) and followed up at community level at 24 hours, 7 days after first visit, and at 6 weeks of life.

Results: Follow up of 6319 newborns were conducted by the ANM (25.4%), ASHAs (4.7%) or both (69.8%); 97% of the babies were followed-up at all the visits. The median duration of follow-ups were 1 day post-discharge, 13th day and 45th days of life. Majority (97%) of them were breastfed, and were warm to touch at the time of the visit. More than 11% of the babies needed referral at every visit. Mortality rate in the cohort of babies discharged from SNCUs till 6 weeks of follow up was 1.5%. Among normal birth weight newborns, it was 0.4% while it was 2.02% among LBW babies. The proportion of girls among those who died increased from 20% in the first follow up to 38.1% at second follow up and 41% at 6 weeks. **Conclusions:** Babies with LBW were at higher risk of death as compared to babies with normal birth weight. Follow-up at critical timepoints can improve survival of small and sick newborns after discharge from SNCUs.

Keywords: *Facility-based care, Mortality, Outcome, Survival.*

***Published online:** January 02, 2021**; PII:** S097475591600271*

India has witnessed a huge increase in facility-based newborn care in the past decade. Since its inception in 2003, there are more than 700 special care newborn units (SNCU) functional across the country [1]. The utilization of services in these units has shown an exponential rise [2]. However, follow-up data of SNCU discharged babies indicates that almost 65% of the mortality is within one month of discharge, majority being during first week after discharge [3]. Follow-up of newborns after discharge from the hospital is therefore crucial. In many low- and middle-income countries (LMICs), the follow-up rate is as low as 8% over the first week of life and 23-65% over the first six weeks [4,5].

The World Health Organization (WHO) recommends that mothers and newborns receive initial postnatal (PNC) care visit within the first 24 hour after delivery and a minimum of three additional PNC visits within 48-72 hours, 7-14 days, and 6 weeks after delivery. Achieving this recommended three clinical visit regimen of care at a 90% level of coverage could avert 18-37% of newborn deaths per year [6]. Evidence from a randomized trial in Kenya suggested that administration of the checklist during home visits increased early recognition of postnatal problems, and increased their likelihood of seeking care for the child [7].

Editorial commentary: Pages 313-14.

In India, Accredited social health activist (ASHA) workers (grassroot level functionaries) are mandated to conduct home visits till 28 days of age. In order to improve contacts with the families and for an extended period, in 2013, the SNCU plus initiative was introduced to facilitate contacts with babies discharged from SNCUs. The Government of India approved an incentive for ASHAs to provide follow up newborn care for babies discharged from SNCU and for LBW newborns every quarter from 3rd month until 1 year of age [3]. The current study reports the survival status and other outcomes among newborns discharged from SNCUs under the SNCU plus initiative.

METHODS

The present study was a retrospective cohort design. The

study was conducted in 13 districts located in four states of Rajasthan, Odisha, Madhya Pradesh and Bihar where the SNCU plus intervention by Norway India Partnership Initiative (NIPI) was carried out with the concurrence of the state governments. The SNCU plus intervention comprised follow-up of SNCU discharged newborns in the community at 24 hours after discharge (first visit), 7 days after first visit (second visit) and 6 weeks after birth (third visit) by ASHAs, and/or Auxiliary Nurse Midwives (ANMs). During each visit, the health care providers recorded weight of the baby, status of feeding (breast/non-human milk), provision of kangaroo mother care (KMC), any illness reported by the mother or detected by the ASHAs/ ANMs based on clinical signs and symptoms in the SNCU plus card. The filled cards were submitted by the health care providers to the block health office where they were entered into a database and stored.

For the purpose of the present study, a trained team of field investigators, extracted the data on a predesigned performa from the SNCU records and SNCU plus cards for all babies who were discharged alive between 2014-16 from the SNCUs in the 13 identified districts where this intervention was implemented. Information on birth weight, gender, reasons for SNCU admission was extracted from SNCU records. The follow-up data was extracted from the SNCU plus cards. In addition, survival and referral data was also extracted from the SNCU plus cards. During the implementation of intervention, KMC practices at home was also monitored in a sub-sample and this data was also utilized for the present study.

Permission from the states and districts were obtained before accessing their data. Since the data were collected and captured by the ASHAs and ANMs as part of the ongoing health programs, informed consent from individual families was not deemed necessary. During the process of data retrieval by our study team, all the identifiers like names of the mothers or fathers and their addresses were masked in order to maintain anonymity.

Statistical analyses: Data were entered in an Excel spreadsheet and analysis was done using SPSS version 21.0. All the key variables were compared between babies with low birthweight (<2500 g) and normal birthweight (≥2500 g) using Chi-square test for proportions and student t test for continuous variables. A $P<0.05$ was considered significant.

RESULTS

For the period 2014 to 2016, follow-up data was available for 6319 newborns who were discharted from SNCUs. The distribution of the available data was 3791 (60%) from Rajasthan, 1101 (17.4%) from Odisha, 972 (15.4%) from Madhya Pradesh and 455 (7.2%) from Bihar.

Data on place of delivery was available for 5678 newborns. It was noted that 5301 (83.9%) had delivered at a government health facility, 282 (4.5%) at private facilities and 95 (1.5%) at home. Two thirds of the neonates whose follow-up data was available were males. Follow-up at home was done by the ANMs (25.4%), ASHAs (4.7%) or both (69.8%). It was noted that 97% of the babies had been

Table I Neonatal Follow-up Indicators After Discharge From Special Newborn Care Units in Four States in India

	Follow-up, n/N (%)		
Indicators	*24 h after discharge*	*7 day after first visit*	*6 wk after birth*
Frequency of breastfeeding			
Birthweight ≥2500 g	2208/2274 (97.1)	2223/2288 (97.1)	2192/2258 (97.1)
Birthweight *<2500 g*	2940/3032 (96.9)	2951/3035 (97.2)	2853/2940 (97.0)
Receiving non-human milk			
Birthweight ≥2500 g	590/2244 (26.3)	594/2247 (26.4)	597/2217 (26.9)
Birthweight <2500 g	703/3014 (23.3)	717/2998 (23.9)	710/2899 (24.5)
Baby warm to touch at the time of visit			
Birthweight >2500 g	2226/2277 (97.7)	2231/2286 (97.6)	2199/2251 (97.7)
Birthweight <2500 g	2963/3030 (97.8)	2960/3032 (97.6)	2865/2938 (97.5)
Babies that needed referral			
Birthweight ≥2500 g	321/2222 (14.5)	287/2225 (12.9)	258/2189 (11.8)
Birthweight <2500 g	509/2944 (17.3)[a]	481/2943 (16.3)[b]	394/2854 (13.8)[c]
No. who had died			
Birthweight >2500 g	2/2263 (0.1)	2/2270 (0.1)	5/2244 (0.2%)
Birthweight <2500 g	8/3013 (0.3)	19/3031 (0.6)[‡]	34/2949 (1.1%)[d]

[a]$P<0.05$; [b]$P=0.02$; [c]$P=0.001$; [d]$P<0.001$.

Table II Follow-up Weights After Discharge From Special Care Newborn Unit in Four States in India

Timepoint	*Birthweight ≥2500g*		*Birthweight <2500g*	
	n	*Weight*	*n*	*Weight*
At birth	2368	2865.1 (307.4)	3162	1948.4 (357.8)
At SNCU discharge	2070	2792.9 (353.2)	2857	1938.8 (431.5)
24 h after discharge	2123	2822.7 (394.6)	2855	2032.5 (623.6)
7 d after first visit	2115	2995.2 (427.6)	2828	2204.9 (513.9)
At 6 wk after birth	2059	3629.4 (702.2)	2715	2864.8 (711.9)

All values in mean (SD); SNCU: Special newborn care unit.

visited at all three time points. The follow up rates in normal and LBW babies were similar. The median interval between the date of discharge and date of first visit was 1 day, and for second and third visit it was the 13th and 45th day after birth, respectively.

Table I compares the key indicators of the newborn on follow-up. A quarter of neonates were receiving non-human milk (mixed feeding) at all follow-up points, which was similar in normal and LBW infants. Significantly more LBW babies needed referral or had died compared to normal weight babies during follow-up till 42 days of life. Among the babies who died, 44 (63.8%) were males. The proportion of girls among those who died increased from 20% in the first follow-up to 38.1% at second follow up and 41% at 6 weeks. **Table II** depicts the weight change in babies during follow-up. A stratified analyses in weight gain by gender did not reveal any significant difference in the two birth weight strata.

Advice on KMC was provided to all the mothers who had a LBW newborn admitted in the SNCU. A sample of 520 new borns discharged from SNCU were followed up during periodic assessments between 2015 to 2017. It was observed (data not shown) that 75% of eligible mothers practiced KMC at home till one month after discharge.

DISCUSSION

A descriptive analysis of a cohort of more than 5000 newborns discharged from SNCUs showed that a large majority of newborns (97%) were followed up at the recommended time points of 24 hours after discharge, at 7 days after first visit and 6 weeks after birth. The mortality among SNCU discharged newborns was 1.5% till 6 weeks of birth with the rates being higher among LBW babies. Also, more LBW babies were in need of referral during follow-up.

The follow-up rates within two weeks after birth in a community hospital from developed nations has been reported to be more than 80% [8,9]. While in USA it included both facility and home visits, in South Africa only facility visits within one week were considered. In LMICs, the follow-up rates were as low as 8-10% [4,5]. In China, only 8% received timely postnatal visit within one week of delivery which increased to 24% till 42 days of delivery [4]. In contrast, it was relatively high (>65%) until 1 year in Tanzania [5]. In India, a large scale nationally representative data in 2007-8 suggests that 45% of the newborns were checked within 24 hours of birth. Around 62% of the babies eventually received two or more check-ups within the first 10 days after birth [10]. Inequalities in receipt of two or more check-ups for the baby before 10 days of life were found to be more pronounced in case of home births.

Quality of home visits, rather than the coverage of visits within 24 hours of birth, play a predominant role in deciding the impact of home visits. It is reported from China that 30-40% of the newborns were weighed and counselled during postnatal visits. However, only 18% were counselled for danger signs [4]. In a study from India on a small sample, it was found that 36% of the mothers were not counselled on newborn care [11]. It is reported that children of mothers who were advised on 'keeping baby warm (kangaroo care) after birth' during their antenatal sessions were significantly less likely to die during the neonatal period compared to those who were not advised about the same [12]. Almost every mother was counselled on KMC, which could account for the lower mortality in the present study.

Mortality rates among sick newborns discharged from facilities varies from 2-4% in different studies. Previous reports from India have suggested that around 10% babies die within one year after discharge from SNCUs [2]. The present analysis gave us much lower rates till 6 weeks of birth. However, this is similar to the independent assessment by the Oxford policy management (OPM) group which noted in 2013 (two years prior to this study) in the same 13 districts of 4 states (*N*=418), 5.7% of new-borns died after discharge from SNCUs. The study also revealed that only 25.7% of newborns discharged from SNCU who were 6 weeks old or more, had received at least three follow up visits by 6 weeks of age [13].

WHAT THIS STUDY ADDS?

- SNCU+ programme is a community-based follow-up of babies discharged from neonatal intensive care units at 24 hours after discharge, 7 days after first visit, and at 6 weeks of life.
- Follow-up at critical timepoints can improve survival of small and sick newborns after discharge from SNCUs.

The study suffers from several limitations. Secondary data available with the health system was utilized for analysis. Since it is a program level data, only key variables, enough to monitor the program, are recorded routinely. The data were retrieved from paper forms and hence there was no check on its completeness or validity. Of the total newborns discharged from SNCUs in 13 districts of 4 states, only 43% were provided home visits under SNCU plus intervention. It is not known if the babies whose records were unavailable were similar to or different from the babies whose records we have. This is a major lacunae that may explain why our rates are different from other studies. Nevertheless, this was a large cohort of more than 6000 babies discharged from SNCUs. Variables like weight at every visit and mortality rates were captured in majority of the cases. Since the data was collected from four different states, we believe the results are more generalizable.

To conclude, newborns discharged from SNCUs, need to be followed up regularly, more so if they are LBW babies, as they are at higher risk of death upto 6 weeks of life. This can improve the overall survival of small and sick neonates discharged from SNCUs.

Acknowledgements: Mr. Ashwani Verma for supporting the cleaning and analysis of SNCU Plus project data.
Contributions: HK has conceptualized the studyand provided overall guidance. AAB and VA guided the data collection process and supervised different steps involved in the study. RK developed the data reporting system, compiled and analyzed the data. SBN reviewed the literature and drafted the manuscript. HK, AAB,RK,PC and PKP provided technical inputs in finalizing the manuscript. All the authors have approved the final version of the manuscript.
Funding: This study was conducted as part of the Newborn care project supported by Norway India Partnership Initiative (NIPI).
Competing interests: None stated.

REFERENCES

1. Ministry of health and Family Welfare. Health Management Information System New Delhi: Ministry of Health and Family Welfare, Government of India; 2017.
2. Neogi SB, Khanna R, Chauhan M, et al. Inpatient care of small and sick newborns in healthcare facilities. J Peri-natol. 2016;36:S18-23.
3. National Health Mission. Revised Guidance note for follow up of LBW and SNCU discharged infants by ASHA New Delhi: Ministry of Health and Family Welfare; 2016.
4. Chen L, Qiong W, van Velthoven MH, et al. Coverage, quality of and barriers to postnatal care in rural Hebei, China: A mixed method study. BMC Pregnancy Childbirth. 2014;14:31.
5. Kanté AM, Chung CE, Larsen AM, Exavery A, Tani K, Phillips JF. Factors associated with compliance with the recommended frequency of postnatal care services in three rural districts of Tanzania. BMC Pregnancy Childbirth. 2015;15:341.
6. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet. 2005; 365:977-88.
7. McConnell M, Ettenger A, Rothschild CW, Muigai F, Cohen J. Can a community health worker administered postnatal checklist increase health-seeking behaviors and knowledge?: Evidence from a randomized trial with a private maternity facility in Kiambu County, Kenya. BMC Pregnancy Childbirth. 2016;16:136.
8. Madlon-Kay DJ, Asche SE. Factors that influence the receipt of well baby care in the first 2 weeks of life. J Am Board Fam Med. 2006;19:258-64.
9. Milambo JPM, Cho K, Okwundu C, et al. Newborn follow-up after discharge from a tertiary care hospital in the Western Cape region of South Africa: A prospective observational cohort study. Glob Health Res Policy. 2018; 3:2.
10. Singh A, Padmadas SS, Mishra US, Pallikadavath S, Johnson FA, Matthews Z. Socio-economic inequalities in the use of postnatal care in India. PLoS One. 2012;7:e37037.
11. Sinha LN, Kaur P, Gupta R, Dalpath S, Goyal V, Murhekar M. Newborn care practices and home-based postnatal newborn care programme - Mewat, Haryana, India, 2013. Western Pac Surveill Response J. 2014;5:22-9.
12. Singh A, Yadav A, Singh A. Utilization of postnatal care for newborns and its association with neonatal mortality in India: An analytical appraisal. BMC Pregnancy Childbirth. 2012;12:33.
13. Impact Evaluation of the Norway India Partnership Initiative Phase-II for Maternal and Child Health. *In*: Limited OPM, editor. Norwegian Agency for Development Cooperation; 2015.

RESEARCH PAPER

Outcome of Children Admitted With SARS-CoV-2 Infection: Experiences From a Pediatric Public Hospital

SUDHA RAO, VRUSHABH GAVALI, SHAKUNTALA S PRABHU, RADHIKA MATHUR, LARISSA ROBERT DABRE, SANJAY B PRABHU AND MINNIE BODHANWALA

From Department of Pediatrics, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India.

Correspondence to: Dr. Sudha Rao, Professor and, Head Department of Pediatrics, Bai Jerbai Wadia Hospital for Children, Acharya Dhonde Marg, Parel, Mumbai, India.
c_sudha@hotmail.com
Received: September 17, 2020; Initial review: October 5, 2020; Accepted: January 10, 2021.

Objective: To study clinical characteristics and outcome of children with admitted to a paediatric hospital in Mumbai, India. **Method**: Review of medical records of 969 children admitted between 19 March and 7 August, 2020, to assess the clinico-demographic characteristics, disease severity and factors predicting outcome in COVID-19 children. Variables were compared between children who were previously healthy (Group I) and those with co-morbidity (Group II). **Results**: 123 (71 boys) children with median (IQR) age of 3 (0.7–6) years were admitted, of which 47 (38%) had co-morbidities. 39 (32 %) children required intensive care and 14 (11.4%) died. Male sex, respiratory manifestation, oxygen saturation <94% at admission, mechanical ventilation, inotrope, hospital stay of <10 days were independent predictors of mortality. Oxygen saturation <94% at admission (OR 35.9, 95% CI 1.5-856) and hospital stay <10 days (OR 9.1, 95% CI 1.04-99.1) were significant. **Conclusion**: COVID-19 in children with co-morbidities causes severe disease. Association of mortality with oxygen saturation by pulse oximeter <94% on admission, and hospital stay <10 days, needs further evaluation.

Keywords: *Co-morbidities, Mortality, Multisystem inflammatory syndrome in children (MIS-C), Prognosis.*

Published online: January 11, 2021; ***PII*:** S097475591600280

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, leading to COVID-19 disease pandemic, has spread all over India and the world. Mumbai Metropolitan Region (MMR) and the City of Mumbai is the worst affected hotspot in India. Our center, a tertiary care, public, specialist hospital, received many children with SARS-CoV-2 from March 19, 2020. Many vulnerable children with co-morbid conditions like heart disease, malnutrition, malignancy, diabetes, chronic kidney disorder, etc. also presented for acute inter current emergencies. This retrospective study presents the demographic, clinical characteristics, treatment and, outcome, care of neonates and children with SARS-CoV-2 positivity from our center.

METHOD

Retrospective medical record review of all children admitted to the hospital between March 19, 2020 and August 7, 2020 was done. Approval of institutional ethics committee obtained. All children with reverse transcriptase-polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 were studied.

As per institutional protocol, derived from national guidelines [1], every child requiring admission was tested by RT-PCR for SARS-CoV-2 from an Indian Council of Medical Research (ICMR) recognized laboratory. Children who tested positive were admitted to the isolation ward, specially created as per national guidelines [2]. Historical details and pre-existing co-morbidities were recorded. COVID-19 disease characterization was done as per guidelines [1]. Multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease (KD) were defined as per standard definition [3,4]. Institutional protocol of care created based on ICMR /GOI recommendations was followed. Some cases of MIS-C/KD included in this study have been previously published [5].

Laboratory investigations and imaging studies were carried as necessary. Therapeutic principles included general supportive therapy, active control of fever, respiratory support with oxygen and/or ventilation as necessary, vasoactive drugs in shock, and active monitoring of organ system dysfunctions. Remdesivir was given to children above 12 years of age with COVID-19 pneumonia. Younger children received it on compassionate grounds with risk explained and an informed consent taken. Intravenous immunoglobulin, pulse methyl-prednisolone, and anticoagulation with low-molecular-weight heparin were used as per protocol. Repeat testing for SARS-CoV-2 PCR and discharge

criteria were followed as per guidelines [1]. Time taken to PCR negativity and duration of hospital stay was noted. Treatment outcomes were defined as discharged or died.

SARS-CoV-2 positive children in this cohort were classified into Group I comprising of previously healthy children, and Group II with children having co-morbidities like heart disease, diabetes, malignancy, malnutrition, renal, hepatobiliary, neurological, surgical/ orthopedic conditions, etc. Variables were compared between the groups.

Statistical analyses: Data was entered in MS Excel, and coded and analyzed in statistical software STATA, version 10.1 (Stata Corp.). Pearson Chi-square test was used for assessing significance of association between outcome (mortality/discharge) and exposure variables/ predictors. Binomial test for difference in proportions was also used to compare proportions in sub-groups or categories in two groups. Student t-test or Mann–Whitney test was performed to assess significance of difference in means or medians in two independent groups. Binary multiple logistic regression model was applied to identify predictors of mortality accounting for the role of other factors, wherein adjusted odds ratio (OR) and 95% Confidence Intervals (CI) were estimated. A *P* value of <0.05 was considered statistically significant for all the comparisons.

RESULTS

Of 969 children admitted during the study period, 123 (12.8%) tested positive for SARS-CoV-2 including 16 (13%) extramural neonates. Five (4.1%) had a history of travel. The median (IQR) age at presentation was 3 (0.7–6.0) year with a male: female ratio of 1.36 (**Table I**).

Seventy six (62%) children belonged to Group I and 47 (38%) Group II. Distribution of underlying illness in Group II is shown in **Fig. 1**. Children with severe COVID-19 had underlying hemato-oncological, renal and cardiac disorders. Children in Group I presented at a younger age than those in Group II [median (IQR) 1.7 (10.5–5.25) vs. 4 (0.8-9) years; *P=0.052*]; 27 (22%) children were asymptomatic. Fever in 24 (20%) or respiratory symptoms in 30 (24%) children were common presenting symptoms, and seizures in 13 (10%) and gastrointestinal symptoms in 15 (12.2%) children were the atypical presentations. Six (5%) children presented with injuries like head injury / limb fracture. Interestingly, severe COVID-19 disease was seen more in Group II whereas MIS-C/KD was more in Group I (**Table I**).

On admission, mean (SD) pulse oximeter saturation (SpO2) and the blood neutrophil: lymphocyte ratio was lower, respectively in Group I than Group II [94.7 (7.1) vs 96.5 (6.1); *P*=0.09] and [2.6 (3.6) vs 4.5 (5.1); *P*=0.09]. Chest radiograph was done in 114 (93%) cases, it was abnormal in 23 (20%) with bilateral haziness, consolidation and pleural effusion being the common abnormalities.

Eighty four (68.3%) children did not require respiratory support. More number of children in Group I (*n*=13/19) required ventilator care. Vasoactive drugs required in 17 (14%) cases and 11were from Group I

Table I Baseline Characteristics, Clinical Profile and Outcome in Children With SARS-CoV-2 Infection (*N*=123)

	All children	*Previously healthy (n=76)*	*With co-morbidity (n=47)*
Male	71 (57.7)	43 (56.6)	28 (59.6)
Age wise distribution			
< 1mo of age	16 (13.0)	12 (15.8)	4 (8.5)
1mo-1 y	31 (25.2)	20 (26.3)	11 (23.4)
1y-5y	39 (31.7)	25 (32.9)	14 (29.8)
5-10 y	26 (21.1)	17 (22.4)	9 (19.2)
>10y[c]	11 (8.9)	2 (2.6)	9 (19.2)
Symptoms at presentation			
Asymptomatic[c]	27 (21.9)	8 (13.2)	19 (36.2)
Fever	24 (19.5)	16 (21.0)	8 (17.0)
Upper respiratory	5 (4.1)	3 (3.9)	2 (4.3)
Lower respiratory	25 (20.3)	18 (23.7)	7 (14.9)
Gastrointestinal	15 (12.2)	12 (15.8)	3 (6.4)
Seizures[b]	13 (10.6)	12 (15.8)	1 (2.1)
Others[b]	14 (11.4)	5 (6.6)	9 (19.2)
Radiology	*n*=114	*n*=73	*n*=41
Abnormal *X*-ray chest	23 (20)	16 (22.0)	7 (27.7)
Disease severity			
Mild[d]	54 (43.9)	50 (65.8)	4 (8.5)
Moderate[d]	26 (21.1)	4 (5.3)	22 (46.8)
Severe[b]	32 (26.0)	14 (18.4)	18 (38.3)
MIS-C/KD[c]	11 (8.9)	8 (10.5)	3 (6.4)
Need for intensive care	39 (31.7)	24 (31.6)	15 (31.9)
Respiratory support			
Only oxygen	20 (16.3)	13 (17.1)	7 (14.9)
Non-invasive ventilation	6 (4.9)	5 (6.7)	1 (2.1)
Invasive ventilation	13 (10.6)	8 (10.5)	5 (10.6)
Vasoactive drugs used	17 (13.8)	11 (14.5)	6 (12.8)
Outcome			
Death	14 (11.4)	6 (7.9)	8 (17.0)
Discharge	105(85.4)	68 (89.5)	37 (78.7)
Still admitted	4 (4)	2 (2.6)	2(4.25)

Values in no. (%) except [a]median (IQR). For comparison between groups [b]P<0.05, [c]P<0.01, [d]P<0.001. MIS-C/KD-Multisystem Inflammatory Syndrome in Children/ Kawasaki disease.

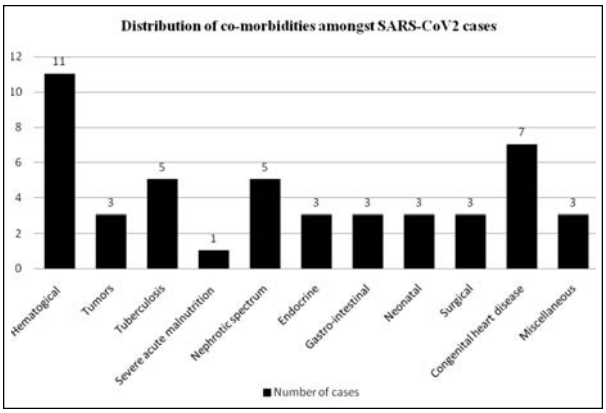


Fig. 1 Distribution of co-morbidities amongst children with SARS-CoV-2 infection.

(**Table I**). Severe COVID-19 pneumonia (*n*=10/39), circulatory collapse (*n*=5/39), MIS-C/KD (*n*=8/39), worsening of underlying disease (*n*=16/39) as indications, 39 (32%) children needed intensive care, which was similar in Groups I and II. Left ventricular dysfunction (*n*=6), dilatation of coronaries (*n*=2) were the echocardiography findings in eight children with MIS-C/KD; 4 (50%) children received IVIG within 48 hours. Remdesivir was given to two children with severe COVID-19 pneumonia.

While compiling the study, 4 children were still admitted. The median duration of PCR negativity was 5 days (range, 3-15 days). 105 (88%) patients were discharged. The median duration of PCR negativity was 5 days (range, 3-15 days); 105 (88%) patients were discharged. The median (range) length of hospital stay was 9 days (4-17 days), which did not differ significantly between Groups I and II (**Table I**).

There were 14 (11.4%) deaths of which 3 (21.5%) were neonates. Four children in Group II who died had underlying malignancy. Male sex, SpO2<94% at admission, abnormal chest *X*-ray, need for respiratory support, need for vasoactive support, need for intensive care and the duration of hospital stay were predictors of mortality on univariate analysis (**Table II**). SpO2<94% at admission [OR (95% CI) 9.1 (1.04–99.1); *P*=0.04] and hospital stay of less than 9 days [OR (95% CI) 35.9 (1.5-856.0); *P*=0.02] were predictors of mortality on regression analysis.

DISCUSSION

The study highlights the clinical characteristics, disease progression, and outcome of 123 children admitted with COVID-19. As admitted children were enrolled, the data likely represents individuals from the moderate-to-severe end of the disease spectrum.

The proportion of previously healthy children was 62%. In a study from Columbia Pediatric COVID-19 management group co-morbidities defined as obesity, asthma, infancy or immune suppression were studied [6].Recent data from US studied chronic lung disease, cardiovascular disease and immune suppression as the common co-morbidities [7].Twenty seven (21.7%) children were asymptomatic comparable to the meta-analysis where 23% were asymptomatic [8]. Initial studies from China reported 4.1-50% cases to be asymptomatic, while 58% were asymptomatic in a study from Pune [9,10].Fever and respiratory symptoms were the common presenting symptoms as also found by others [8-10]. Atypical presentations like seizures (10.6%), gastrointestinal symptoms (12.2%) were more common in this series as compared to other studies[7,10,11]. More children in our cohort had severe disease as compared to only 1% as reported in recent retrospective study from China[12].Children with underlying hemato-oncological, renal or cardiac disorders had severe disease. Interestingly, the immune response of COVID-19, the MIS-C/KD was found more in Group I than Group II. This has been reported in other studies also[5,13].Presence of comorbidity dysregulates or blunts the immunological host responses causing severe infection but a hyper-inflammatory immune response like MIS-C/KD is not seen.

Table II Predictors of Outcome in Pediatric Inpatients With SARS-CoV-2 Infection (*N*=119)

Factors	*Death (n=14)*	*Discharge (n=105)*	*OR 95% CI*
Age at presentation ≥3 y	7 (50)	56 (88.9)	0.88 (0.24- 3.15)
Male sex[a]	11 (78.6)	58 (55.2)	4.52 (1.1-26.4)
Asymptomatic	0	27 (25.7)	-
Respiratory symptoms [a]	10 (71.4)	41 (39.1)	-
Normal *X*-ray chest,[b] *n*=110	5 (35.7)	82 (80)	7.2 (1.9-29.7)
SpO2 <94% at admission[b]	8 (57.1)	15 (14.3)	8.0 (2.0-31.6)
Respiratory support[b]	12 (85.7)	25 (23.8)	19.2 (3.8- 182.5)
Use of vasoactive drugs	7 (50.0)	10 (9.5)	19.5 (2.3- 38.5)
Need for intensive care[b]	12 (85.7)	26 (24.8)	18.2 (3.6- 173.2)
Hospital stay ≥9 d	7 (87.5)	43 (50.0)	7 (0.8- 322.6)

All values in no. (%); [a]P<0.05, [b]P=0.001.

WHAT IS ALREADY KNOWN?

- Neonates, male gender, pre-existing medical conditions, fever, lower respiratory tract infection, radiological changes suggestive of pneumonia or ARDS, and viral co-infection were associated with more severe course.

WHAT THIS STUDY ADDS?

- Children with underlying medical illnesses have significantly severe COVID-19 disease.
- Male gender, hypoxia (SpO2 <94%) on admission, need for respiratory support, need for vasoactive drugs, ICU care, and length of hospital stay of <10 days is significantly associated with mortality.

Need for intensive care in our series is similar to that reported in literature [14]. Adult studies suggest presence of co-morbidities as an important predictor of need for intensive care[15], which was not found by us. Children requiring mechanical ventilation (15.5%) were fewer than the cohort from USA [6,16] as we had more non-respiratory presentations.

A study of children from the European cohort concluded that neonates, male sex, pre-existing medical conditions, fever, lower respiratory tract infection, radiological changes of pneumonia or ARDS, and viral co-infection were associated with more severe course on univariate analysis; however, these were not correlated to mortality [11]. In our cohort, male sex, hypoxia (SpO2 <94%) on admission, need for respiratory support, inotropes, intensive care, length of hospital stay <10 days was significantly associated with mortality. Male gender has been associated with a higher risk of severe disease and mortality because of higher ACE-2 receptor expression [17]. On regression analysis, SpO2 <94% on admission and length of hospital stay of <10 days were predictors of mortality and not the presence of co-morbidities. This need to be corroborated with a bigger sample size. Experience from adult studies has shown mortality within 1 to 2 weeks of ICU admission [15].

As a retrospective study, certain important parameters like onset of symptoms from day of contact, source of infection, and exact duration of COVID-19 RT-PCR positivity in all children could not be assessed.

To conclude, pediatric COVID-19 although considered a mild illness, children with co morbidity manifest with severe disease. Male sex, hypoxia on admission, need for intensive care, ventilator support, inotrope, hospital stay of <10 days are predictors of mortality. Policy of testing all admitted children for COVID-19 helps identify and segregate the cases, provide protocol based care, characterize the severity, initiate prompt treatment and improve outcome.

Contributors: SR,SSP,SBP: conceived, designed the study, finalised the manuscript; SR,VG,RM, LRD,SBP,SSP,MB: data collection, data analysis; SR,VG,RM,LRD,SSP,SBP: Literature search, interpretation of data, writing manuscript. All authors approved the final manuscript.

Ethics clearance: Institutional Ethics Committee Bai Jerbai Wadia Hospital for Children; No. IEC-BJWHC/ 89/2020, dated 26 August, 2020.

Funding: None; *Competing interests:* None stated.

REFERENCES

1. Directorate General of Health Services. Revised National Clinical Management Guideline for COVID-19. New Delhi (IN): Ministry of Health & Family Welfare. Available at www.mohfw.gov.in.
2. National Centre for Disease Control. COVID -19 Outbreak Guidelines for Setting up. New Delhi (IN): Ministry of Health & Family Welfare. Available at www.mohfw.gov.in.
3. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20:e276-88.
4. Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. Int J Rheum Dis. 2018;21:36-44.
5. Shobhavat L, Solomon R, Rao S, et al. Multisystem inflammatory syndrome in children: Clinical features and management—Intensive care experience from a pediatric public hospital in Western India. Indian J Crit Care Med. 2020; 24: 1089–94.
6. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr. 2020;174:e202430.
7. De Luca CD, Esposito E, Cristiani L, et al. Covid-19 in children: A brief overview after three months experience. Paediatr Respir Rev. 2020; 35:9-14.
8. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of sars-cov-2 infection in children: A systematic review and meta-analysis. Indian Pediatr. 2020;57: 820-26.
9. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020 ;145:e20200702
10. Sarangi B, Reddy VS, Oswal JS, et al. Epidemiological and clinical characteristics of COVID-19 in Indian children in the initial phase of the pandemic: A cross-sectional study. Indian Pediatr. 2020; 57:914-17.
11. Götzinger F, Santiago-García B, Noguera-Julián A, et al.

COVID-19 in children and adolescents in Europe: A multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4:653-61.
12. Guo CX, He L, Yin JY, et al. Epidemiological and clinical features of pediatric COVID-19. BMC Med. 2020;18:250.
13. Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Clinical presentation, infectivity, and immune responses. J Pediatr. 2020;227:45-52.
14. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. Morb Mortal Wkly Rep. 2020;69:1081-88.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
16. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020;174:868-73.
17. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215: 108427.

RESEARCH PAPER

Analysis of Young Infant Deaths Using Verbal Autopsies and Accuracy of Verbal Autopsy Tool in Chennai, India

R USHA DEVI, S MANGALA BHARATHI AND J KUMUTHA

From Department of Neonatology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, India.

Correspondence to:
Dr Mangala Bharathi S, Professor, Department of Neonatology, Institute of Child Health and Hospital for Children, Madras Medical College, Egmore, Chennai 600 008, India.
drmangalabharathi@gmail.com
Received: January 01, 2020;
Initial review: February 26, 2020;
Accepted: January 15, 2021.

Objective: To identify medical and non-medical factors associated with young infant deaths using verbal autopsies and to evaluate the validity of state verbal autopsy tool in identifying medical causes. **Design:** Descriptive study to report factors associated with young infant deaths, and diagnostic accuracy study of the verbal autopsy tool. **Results:** Prematurity related illnesses were the major contributors to mortality. Deliveries were predominantly in health care facilities (99%); lower maternal education (11.2%), lesser birth spacing (80%), and higher birth order (7.5%) were other factors noted. Verbal autopsy questionnaire had a diagnostic accuracy of ≥95% in identifying major causes of death (kappa value 0.8-1.0). **Conclusion:** Current state verbal autopsy tool is valid in identifying causes of death.

Keywords: *Infant mortality, Newborn death, Still birth, Janani suraksha yojna.*

India contributes to 22% of the global burden of under-5 deaths and nearly half of it are neonatal deaths [1,2]. Routine registration systems do not provide all information on causes of death and the contributory factors. This affects strategy planning as well as implementation of programs [2,3]. In such situations, detailed child death review using verbal autopsy tool will be of great help. Lack of a standardized verbal autopsy instrument and administration methods are key challenges that remain unresolved [4].

This study was conducted to identify factors associated with young infant deaths using State verbal autopsy questionnaire as a tool, and to evaluate its accuracy in determining major causes of death.

METHODS

All young infant deaths (<2 months) between April, 2013 to March, 2015 within Chennai Corporation zones were included in the study. Investigation of these deaths was done using State verbal autopsy forms. Maternal characteristics recorded comprised of socio-demographic, pregnancy and delivery details. Infant characteristics comprised of gender, birth weight, gestational age, age at death, place of death and cause of death. For neonatal deaths and post neonatal deaths, there were set of questions under each cause of death (as per ICD-10 classification). Depending upon the answers, one of the major causes was selected. The tool was used by field workers. They were provided a structured training for two weeks where each question in the tool and possible responses were discussed.

Clinical summaries of babies were collected from health posts near their residence. Clinical diagnosis was considered as the gold standard. The disease pathology which led to deterioration of the baby and death was taken as main cause of death. For home deaths, diagnosis on arrival to hospital or in death certificate was taken.

Statistical analyses: We used descriptive statistics to describe baseline variables. Diagnostic test was used to estimate sensitivity, specificity, positive predictive value and negative predictive value of verbal autopsy tool taking hospital diagnosis as gold standard. Kappa statistics was used to study agreement between verbal autopsy and clinical diagnosis at different time periods after death [5]. We used statistical software package SPSS version 13.0 for analyses.

RESULTS

Of 164009 live births during the study period, there were 865 young infant deaths, accounting for a mortality rate of 5.2 per 1000 live births. Of these, we could access only 629 records (**Fig. 1),** 319 in 2013-14, and 310 in 2014-15.

Consanguinity was noted in 20% of these babies. Most mothers (95%) had ≥3 antenatal visits. 193 (31%) mothers had some antenatal illness, pregnancy induced hypertension (14.1%) being the most common followed by anemia (6.4%) and diabetes (5.9%).

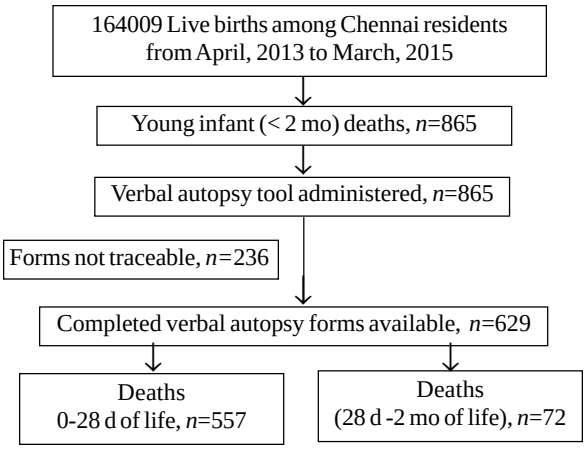


Fig. 1 Flow diagram of the study.

Two third of the babies were low birthweight. More than 99% of the deliveries were institutional. Among the neonatal deaths, care was sought within 24 hours of identifying illness in majority (75%) (**Table I**). Most of the babies who died were preterm (55%) with 11.5% being extremely low birthweight. The single most important cause assigned was asphyxia (27%) followed by respiratory distress syndrome (20%), sepsis (17%), congenital malformations/surgical cases (15%), extreme prematurity (9%), heart disease (6%) and multiple congenital anomalies (3.5%).

According to verbal autopsy tool, asphyxia (32%) was the single major cause of death followed by sepsis and respiratory distress (17% each), congenital anomalies (8%) and heart disease (6%); 10% of deaths were attributed to prematurity alone. Around 30% of neonatal deaths happened within 24 hours of life. There were 50 home deaths (5.7% of total deaths), 66% of which happened between 6 PM and 6 AM (**Table I**).

Diagnostic accuracy of verbal autopsy tool in identifying major causes of death was more than 95%. In the diagnosis of prematurity, positive predictive value was low (77%). Verbal autopsy tool had good agreement in all the major causes with kappa values ranging from 0.82-0.90 (**Table II**).

Only 21.9% of the verbal autopsy tool had been administered within 14 days of death 21.4% were done between 14 and 30 days and 32.9% after 30 days (maximum time of administration, 360 days). Date was not mentioned in 24% of the questionnaires. The sensitivity, specificity, positive, negative predictive values and kappa agreement in our study was equally good across various timeframes. However, the positive predictive value for the diagnosis of prematurity was low and kappa agreement for the same was moderate (**Supp. Table I**).

Table I Delivery Characteristics, Health Seeking Behavior, Access to Health Facilities and Analysis of Home Deaths (*N*=629)

Characteristics	*No (%)*
Normal delivery	354 (56.2)
Place of delivery[a]	
Level 1	86 (13.7)
Level 2	46 (7.3)
Level 3	497 (79)
Maturity	
≤28 wk	84 (13.4)
28-37 wk	264 (42)
>37 wk	281 (44.6)
Birthweight	
<1 kg	72 (11.4)
1-1.5 kg	119 (18.9)
1.5-2.5 kg	209 (33.3)
>2.5 kg	229 (36.4)
Illness recognized by parents	58(9.2)
Duration of illness prior to seeking care	
<24 hr	187 (29.8)
1-3 d	155 (24.6)
>3 d	287 (45.6)
Health seeking behavior	
Yes	609 (96.8)
Transport mode (n=144)	
108 neonatal	102 (70.8)
108 general	10 (6.9)
Private ambulance	22 (15.2)
Travelling time (*n* = 144) <1 h	89 (61)
Analysis of home deaths (*n*=50)	
Birthweight	
<1.5 kg	2 (4)
1.5-2.5 kg	14 (28)
>2.5 kg	34 (68)
Postnatal age at death	
<7 d	9 (18)
7-28 d	25 (50)
>28 d	16 (32)
Female	30 (60)
Cause of death	
Sudden infant death syndrome (SIDS)	29 (58)
Aspiration	15 (30)

Data represented as no. (%); [a] home delivery in 1.

DISCUSSION

High institutional deliveries noted in the study can be attributed to government programs providing financial assistance to pregnant women like Janani Suraksha

WHAT THIS STUDY ADDS?

- The State verbal autopsy has a good accuracy in ascertaining causes of death and also brings out the improvement in non-medical factors, health care services and health-seeking attitude over the years.

Table II Accuracy of Verbal Autopsy Tool Compared With the Gold Standard (*N*=629)

Diagnosis	*Sensitivity*	*Specificity*	*AUC*	*Kappa*
Birth asphyxia *n*=171	94.2% (89.5-97.2)	96.9% (94.9-98.3)	0.96 (0.94- 0.97)	0.9 (0.86-0.94)
RDS + MAS *n*=137	82.5% (75.1-88.4)	99.2% (97.9-99.8)	0.91 (0.88-0.94)	0.86 (0.81-0.91)
Neonatal sepsis *n*=108	90.7% (83.6-95.5)	97.5% (95.8-98.7)	0.94 (0.91- 0.97)	0.87 (0.82-0.92)
Prematurity *n*=55	92.7% (82.4-98.0)	97.4% (95.7-98.5)	0.95 (0.92- 0.99)	0.82 (0.75-0.90)

Values in measure (95% CI); Pooled diagnostic accuracy was 92.2%. and Kappa of 0.90 (0.87-092); AUC: Area under the curve, RDS: Respiratory distress syndrome, MAS: Meconium aspiration syndrome.

Yojana (JSY) and Janani Shishu Suraksha Karyakaram (JSSK) [6,7].

Majority of deaths happened in the first three days after birth, similar to other studies [8,9], which is directly related to antenatal, intra partum and immediate neonatal care. Health-seeking behavior of the parents has undergone a marked improvement when compared to previous studies [10]. Access to transport has significantly increased because of 108 neonatal services, which has helped in timely stabilization and treatment. In the Million Death Study, the major causes of death were prematurity, neonatal infections and birth asphyxia [11]. Prematurity-related illnesses were the major contributors in our study as well.

In many studies, the diagnosis of asphyxia is collated into the prematurity complications, if gestation is less than 34 weeks [12]. Currently, most studies based on verbal autopsy assign a single underlying cause of death [13]. However, some experts have suggested that this may not be the most appropriate strategy and multiple causes of deaths should be considered [14].

As a survey methodology, there is reason to believe that recall bias may affect the validity of verbal autopsy. WHO recommends that, after a period of mourning, the verbal autopsy be conducted as soon as possible, and recalls of more than one year should be interpreted with caution [15]. We found good agreement at different periods of administration and thus every effort should be made to fill the questionnaire even if 14 days have elapsed since death.

Limitations of the study include lack of separate set of questions in this tool for marking cause of death as prematurity or respiratory distress syndrome, and its inability to assign more than one cause of death. Missing verbal autopsy forms could also have influenced the results of the study. The limitations of medical records as a gold standard needs to be recognized as case records may be incomplete and relevant investigations may be missing.

We found State verbal autopsy tool valid in identifying most of the common medical causes of young infant deaths. We recommend incorporating this verbal autopsy tool even in hospital death audits to capture significant non-medical contributing factors.

Ethics Clearance: Institutional ethics committee Madras Medical College, Chennai; No. ECR/ 270/Inst./TN/2013/No.10012017, dated January 3, 2017.
Contributors: UDR: design of study, data collection, data analysis, interpretation, manuscript writing and draft preparation; MBS: data interpretation, design, critical editing and draft preparation; KJ: data interpretation, design, critical editing and draft preparation. All the authors contributed to drafting of the manuscript and approved the final version of the manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet. 2003;361:2226-34.
2. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365:891-900.
3. Lawn JE, Wilczynska-Ketende K, Cousens SN. Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol. 2006;35:706-18.
4. Thatte N, Kalter HD, Baqui AH, Williams EM, Darmstadt GL. Ascertaining causes of neonatal deaths using verbal autopsy: current methods and challenges. J Perinatol. 2009;29:187-94.
5. Viera AJ, Garrett JM. Understanding interobserver

agreement: The kappa statistic. Fam Med. 2005;37:360-3.
6. Lim SS, Dandona L, Hoisington JA, James SL, Hogan MC, Gakidou E. India's Janani Suraksha Yojana, a conditional cash transfer programme to increase births in health facilities: An impact evaluation. Lancet. 2010;375:2009-23.
7. Tripathi N, Saini SK, Prinja S. Impact of Janani Shishu Suraksha Karyakram on out-of-pocket expenditure among urban slum dwellers in northern India. Indian Pediatr. 2014;51:475-7.
8. Baqui AH, Darmstadt GL, Williams EK, et al. Rates, timing and causes of neonatal deaths in rural India: Implications for neonatal health programmes. Bull World Health Organ. 2006;84:706-13.
9. Bapat U, Alcock G, More NS, Das S, Joshi W, Osrin D. Stillbirths and newborn deaths in slum settlements in Mumbai, India: A prospective verbal autopsy study. BMC Pregnancy and Childbirth 2012;12:39.
10. Bhandari N, Bahl R, Taneja S, Martines J, Bhan MK. Pathways to infant mortality in urban slums of Delhi, India: implications for improving the quality of community- and hospital-based programmes. J Health Popul Nutr. 2002;20:148-55.
11. Million Death Study Collaborators, Bassani DG, Kumar R, Awasthi S, et al. Causes of neonatal and child mortality in India: A nationally representative mortality survey. Lancet. 2010;376:1853-60.
12. Soofi SB, Ariff S, Khan U, et al. Diagnostic accuracy of WHO verbal autopsy tool for ascertaining causes of neonatal deaths in the urban setting of Pakistan: A hospital-based prospective study. BMC Pediatr. 2015;15:144.
13. Edmond KM, Quigley MA, Zandoh C, et al. Diagnostic accuracy of verbal autopsies in ascertaining the causes of stillbirths and neonatal deaths in rural Ghana. Paediatr Perinat Epidemiol. 2008;22:417-29.
14. Anker M. The effect of misclassification error on reported cause-specific mortality fractions from verbal autopsy. Int J Epidemiol 1997;26:1090-6.
15. Manual for the training of interviewers on the use of the 2016 WHO VA instrument. World Health Organization; 2017.

Supplementary Table I Accuracy of Verbal autopsy Based on Day of Verbal Autopsy (*N*=629)

Diagnosis	*Sensitivity*	*Specificity*	*AUC*	*Kappa*
< 14 d [a], n=138 (21.9)				
Birth asphyxia *n*= 39	89.7% (75.8-97.1)	100% (96.3-100)	0.95 (0.90-1.00)	0.9 (0.85-99)
RDS+ MAS *n*= 24	87% (66.4-97.2)	100% (96.8-100)	0.94 (0.87-1.00)	0.92 (0.82-1)
Neonatal sepsis *n*= 27	96.3% (81-99.9)	97.3% (92.3-99.4)	0.97 (0.93-1.00)	0.91 (0.82-1)
Prematurity *n*= 7	85.7% (42.1-99.6)	96.2% (91.3-98.7)	0.91 (0.77-1.00)	0.64 (0.38-0.91)
14 d-1mo [b], n=135 (21.4)				
Birth asphyxia n= 30	93.3% (77.9-99.2)	97.1% (91.9-99.4)	0.95 (0.90-1.00)	0.89 (0.80-0.99)
RDS+ MAS n= 34	79.4% (62.1-91.3)	100% (96.4-100)	0.90 (0.83-0.97)	0.85 (0.73-0.96)
Neonatal Sepsis n= 25	96% (79.6-99.9)	95.5% (89.7-98.5)	0.96 (0.91-1.00)	0.86 (0.75-0.97)
Prematurity n= 13	100% (75.3-100)	99.2% (95.5-100)	1.00 (0.99-1.00)	0.96 (0.87-1.0)
>1 mo [c], n=207 (32.9)				
Birth asphyxia n= 49	95.9% (86-99.5)	94.9% (90.3-97.8)	0.95 (0.92-0.99)	0.87 (0.79-0.95)
RDS+ MAS n= 47	80.9% (66.7-90.9)	99.4% (96.6-100.0)	0.90 (0.84-0.96)	0.85 (0.76-0.94)
Neonatal sepsis n= 41	85.4% (70.8-94.4)	98.2% (94.8-99.6)	0.92 (0.86-0.97)	0.86 (0.77-0.95)
Prematurity n= 25	96% (79.6-99.9)	96.7% (93-98.8)	0.96 (0.92-1.0)	0.85 (0.75-0.96)

Values in measure (95% CI); AUC – Area under the curve, RDS – Respiratory distress syndrome, MAS – Meconium aspiration syndrome; Kappa coefficient for pooled data a0.90 (0.85-0.96), b0.90 (0.84-0.96), c0.88 (0.83-0.93),

RESEARCH PAPER

Clinical Manifestations and Outcome of Scrub Typhus in Infants From Odisha

JYOTI RANJAN BEHERA,[1] SANJAY KUMAR SAHU,[1] NIRANJAN MOHANTY,[1] NIRMAL KUMAR MOHAKUD[1] AND AMOS LAL[2]
From [1]Department of Pediatrics, Kalinga Institute of Medical Sciences, KIIT Deemed University, Bhubaneswar, India; and [2]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, MN, USA.

Correspondence to:
Dr Nirmal Kumar Mohakud,
Professor,
Department of Paediatrics,
Kalinga Institute of Medical Sciences,
KIIT Deemed to be University,
Bhubaneswar, India.
nirmal.mahakud@kims.ac.in
Received: August 10, 2020;
Initial review: August 11, 2020;
Accepted: December 31, 2020.

Objective: To study manifestations and outcome of scrub typhus in infants. **Methods:** Case record analysis of infants with scrub typhus admitted to a tertiary care hospital, diagnosed by IgM ELISA from January 1, 2016 to December 31, 2019. **Results:** Out of 374 children diagnosed with scrub typhus, 34 (9%) were infants. Chief presentation were fever 34 (100 %), feeding difficulty 24 (70.6%), lethargy 18 (52.9%) and irritability 15 (44.1%). Clinically, pallor 30 (88.2%), tachycardia 29 (85.3%), tachypnea 24 (70.6%), hepatosplenomegaly 30 (88.2%) and eschar 6 (17.6%) were detected. Significant laboratory parameters were anemia 33 (97.1%), leukocytosis 33 (97.1%), thrombocytopenia 17 (50%) and transaminitis 21 (63.6%). Pneumonia 18 (52.9%) was noticed as the major complication. Infants requiring intensive care 17(50%) had characteristic thrombocytopenia, hypoalbuminemia and transaminitis (P<0.05). They recovered well with doxycycline. **Conclusion:** Manifestation of scrub typhus in infants tends to be severe with combination of hematologic, pulmonary and hepatic involvement requiring intensive care. The response to doxycycline is good.

Keywords: *Doxycycline, Eschar, Intensive care, Rickettsia.*

Scrub typhus is an emerging rickettsial infectious disease over the past 8-10 years affecting all age groups and having a wide geographical distribution. Most clinical features mimic common tropical febrile infectious diseases making the diagnosis difficult [1]. Various life-threatening complications resulting from multi-organ dysfunction usually occur in the second week of illness [2]. Eschar is the hallmark of scrub typhus, but the incidence in infants is not known. Ample number of studies are available on different aspects of scrub typhus in children, but not in infants. This study aimed to find out the manifestations and outcome of infants with scrub typhus. The laboratory parameters influencing the need for intensive care were also determined.

METHODS

This was a retrospective observational study conducted in infants with a diagnosis of scrub typhus admitted in the pediatric ward of a tertiary care teaching hospital of Eastern Odisha from January, 2016 to December, 2019. Scrub typhus was suspected in infants who presented with acute fever (>5 days) and confirmed by IgM ELISA using INBIOS kit (In BiOS International Inc., which is 99.9% sensitive and 99.15% specific [3]. Reports with optical density of >0.5 at 450 nm were taken to define case positivity. The difference in manifestation and outcome of infant scrub typhus from older children were considered as the primary outcome and laboratory parameters influencing intensive care requirement as the secondary outcome, respectively.

Data including age, sex, residential area, duration of fever, associated symptoms, vitals with general and systemic examination findings were documented. Complete blood counts, chest *X*-rays, rapid antigen test for malaria, dengue (NS1 antigen and IgM antibody) test, urine and blood cultures, serum urea and creatinine, C-reactive protein (CRP), liver function tests (LFT), electrolytes and other relevant investigations and treatment provided were collected from the records. Complications, end organ dysfunction, the need for intensive care and mechanical ventilation were also noted. Infants with features of end organ dysfunction were admitted to the pediatric intensive care unit (PICU) [4]. Management of the patients was based on the standard IAP guidelines on 'Diagnosis and Management of Scrub Typhus in India'. Doxycycline was administered in the dose of 2.2 mg/ kg twice daily till 3 days after subsidence of fever or for a total of 7 days. Severe and/or complicated cases were given 10 days therapy. Alternatively, Azithromycin was used in the dose of 10 mg/kg/day for 5 days [1].

Descriptive statistics were calculated. Laboratory

WHAT THIS STUDY ADDS?

- Infants with scrub typhus have predominant hepatic, pulmonary and hematological involvement.

parameters of infants requiring intensive care were compared with those not requiring. The data were analyzed using SPSS version 2.0. *P* value <0.05 was considered statistically significant. Approval of the institutional ethical committee (IEC) was obtained before initiation of the study.

RESULTS

Infants constituted 34 (9.1%) of the 374 cases of scrub typhus cases admitted during the study period of 3 years. Out of these, 18 (52.95%) were under 6 months, and 16 (47.05%) were between 7 months to 1 year of age. The mean (SD) age of infants was 6.4 (3.6) months, the youngest being 38 days old. There was a male 23 (67.7%) predominance. Majority of infants 25 (73.53%) were from rural background.

Common clinical symptoms were fever 34 (100%), poor feeding 24 (70.59%), lethargy 18 (52.94%), respiratory symptoms 16 (47.07%), irritability 15 (44.12%), seizure 8 (23.53%) and rash 6 (17.65%). On examination, the key findings were pallor 30 (88.24%), hepatosplenomegaly 30 (88.26%), tachycardia 29 (85.29%), tachypnea 24 (70.57%) and meningeal signs 4 (11.76%). Eschar was found in 6 (17.65%) infants. Characteristic laboratory findings were anemia (Hb <10.5 gm%), leukocytosis (TLC >14000/mm^3) and raised C Reactive Protein (CRP>6 mg/dL) in 33 (97.06%) infants. Transaminitis (AST & ALT >2 times) 21 (63.63%), thrombocytopenia (<1.5 lacs/mm^3) 17 (50%), hypo-natremia (<135 meq/L) 13 (39.39%), hypoalbuminemia (<2.5 gm/dL) 9 (27.27%) were other significant lab findings. Common complications seen were, pneumonia 18 (52.94%) and meningoencephalitis 7 (20.58%). Acute respiratory distress syndrome (ARDS), septic shock and multi organ dysfunction syndrome (MODS) were found in 4 (11.76%) cases each whereas Haemophagocytic Lymphohistiocytosis (HLH) was seen in 1(2.9%) patient.

Intensive care (ICU) was needed in 17 (50%) infants, of which 5 (14.71%) required mechanical ventilation. **Table I** compares laboratory parameters among infants of PICU and non-PICU group. Significant parameter were hypoalbuminemia (*P*=0.001), transaminitis (*P*=0.03) and thrombocytopenia (*P*<0.001). The mean value of scrub typhus IgM in PICU admitted infants was 1.89 as compared to non PICU admitted infants which was 1.11 (*P*=0.003). Of note, mean (SD) CRP of the infants admitted in PICU was 80.03 (42.55) mg/dL compared to the non PICU group was 59.49 (29.14) mg/dL (*P*=0.08).

Along with supportive treatment, doxycycline was administered to 30 (88.23%), Azithromycin to 3 (8.82%) and both Doxycycline and Azithromycin were administered to 1 (2.94%) case. All ICU patients received IV/oral doxycycline. No adverse events were noticed following doxycycline administration in infants. The mean (SD) for defervescence was 2.23 (1.72) days. The median (IQR) hospital stay was 7 (5-8) days with a range of 4 to 20 days. Out of 34 infants, 33 (97%) were discharged and one left against medical advice. There was no mortality.

DISCUSSION

Our study focuses on different aspects of scrub typhus in infants. Major clinical findings observed in our study like fever, lethargy, poor feeding, tachycardia, tachypnea and hepatoslenomegaly are similar to malaria, dengue, enteric fever and sepsis in this age group. Hence scrub typhus should be an important differential diagnosis in febrile infants. Various studies in older children have documented eschar in 40-90% of cases [5,6]. Age-wise distribution of eschar observed by Rose, et al. [6] were 54.5%, 31.9% and 13.6% in <5, 6-10 and 11-15 years age group, respectively. However, no exclusive data is available for infants [6]. One report from Odisha has observed 17.9% of older children with scrub typhus had eschar [7]. Similarly, our study has found eschar in 17.65% of infants with scrub typhus. Due to its uncommon occurrence in the infants, the diagnosis should however not be discarded in the absence of eschar.

We have compared several parameters from different studies of scrub typhus in children above 1 year from various parts of Indian subcontinent with the present

Table I Laboratory Parameters Among Infants With Scrub Typhus With or Without Need of Intensive Care

Parameter	*Non-PICU group, n=17*	*PICU group, n=17*
Anemia	17 (100)	16 (94.1)
Leucocytosis	17 (100)	1694.11
Thrombocytopenia[a]	4 (23.52)	13 (76.5)
Hypoalbuminemia[a]	1 (5.9)	8 (47.0)
Hyponatremia	5 (29.4)	8 (47.0)
Transaminitis[b]	7 (41.2)	14 (82.3)
High c-reactive protein	16 (94.1)	17 (100)

Values in no. (%). PICU-Pediatric intensive care unit; [b]levels greater than twice normal.[a]P<0.001.

study. Anemia and leucocytosis were the key haematological abnormalities, which were significantly higher than those observed by others. However, the incidence of thrombocytopenia was comparable [2,8]. Transaminitis denotes hepatic involvement and its incidence was higher in our study when compared to scrub typhus in older children [9,10]. More than half of infants (52.94%) developed pneumonia, However the incidence in older children has been reported to be around 11%; thus signifying pulmonary predilection in infants. Pathak, et al. [11] found very high incidence AKI (65.8%) and myocarditis (75.4%) in 1-16 years age group but these findings were negligible in infants as in the present study. HLH, a rare complication was observed in only 1 case which also recovered on treatment of the underlying disease. Intensive care was required in 50% infants which was higher as compared to older children [9,11]

Thrombocytopenia, transaminitis, hypoalbuminemia and higher IgM titer by ELISA were significant findings while comparing PICU and non PICU infants (*P* value<0.05). Hence these parameters may be considered as markers of severity in infant with scrub typhus. Although CRP values were not found statistically significant in these two groups, there was a trend towards higher CRP in the intensive care groups. The mean (SD) defervescence period and median (IQR) hospital stay were similar to other studies in older children [13,14].There was no mortality in our study, whereas mortality in older children ranged from 9-12% in literature [10,15]. Smaller sample size and retrospective nature were the major limitations of this study. Scrub typhus should be considered as a differential diagnosis for unremitting fever in infants. Significant hepatic, pulmonary and hematological involvement would indicate the requirement of intensive care in infants. Eschar, the hallmark of the disease may not be always present in infants. Hence increase awareness of early diagnosis and treatment will significantly help in decreasing the mortality and improving the prognosis in this vulnerable age group.

Ethical clearance: Institutional ethics committee of KIMS; No. : KIIT/KIMS/IEC/339/2020, dated July 28, 2020.

Acknowledgement: Dr Mona Pathak, statistician, for her help in analysis of the data. Dr Mirabai Das for her help in grammatical correction.

Contributors: NM, NKM: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; JB, AL and SS: designed the data collection instruments, collected data, carried out the initial analyses, reviewed and revised the manuscript. All authors approved the final manuscript.

Funding: None; *Competing interests:* None stated.

REFERENCES

1. Rathi N, Kulkarni A, Yewale V; For Indian Academy of Pediatrics Guidelines on Rickettsial Diseases in Children Committee. IAP Guidelines on Rickettsial Diseases in Children. Indian Pediatr. 2017;54:223-9.
2. Kumar M, Krishnamurthy S, Delhikumar CG, Narayanan P, Biswal N, Srinivasan S. Scrub typhus in children at a tertiary hospital in southern India: Clinical profile and complications. J Infect Public Health. 2012;5:82-8.
3. Pote K, Narang R, Deshmukh P. Diagnostic performance of serological tests to detect antibodies against acute scrub typhus infection in central India. Indian J Med Microbiol. 2018;36:108-12.
4. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics. Pediatr Crit Care Med. 2005;6:2-8.
5. Pradeepan JA, Ketheesan N, Murugananthan K. Emerging scrub typhus infection in the northern region of Sri Lanka. BMC Res Notes. 2014;7:1-4.
6. Rose W, Rajan RJ, Punnen A, Ghosh U. Distribution of eschar in pediatric scrub typhus. J Trop Pediatr. 2016;62:415-20.
7. Bal M, Mohanta MP, Sahu S, Dwibedi B, Pati S, Ranjit M. Profile of pediatric scrub typhus in Odisha, India. Indian Pediatr. 2019;56:304-6.
8. Kumar Bhat N, Dhar M, Mittal G, et al. Scrub typhus in children at a tertiary hospital in north India: Clinical profile and complications. Iran J Pediatr. 2014;24:387-92.
9. Ganesh R, Suresh N, Pratyusha LL, Janakiraman L, Manickam M, Andal A. Clinical profile and outcome of children with scrub typhus from Chennai, South India. Eur J Pediatr. 2018;177:887-90.
10. Nallasamy K, Gupta S, Bansal A, et al. Clinical profile and predictors of intensive care unit admission in pediatric scrub typhus: A retrospective observational study from north India. Indian J Crit Care Med. 2020;24:445-50.
11. Pathak S, Chaudhary N, Dhakal P, et al. Clinical profile, complications and outcome of scrub typhus in children: A hospital based observational study in central Nepal. PLoS One. 2019;14:e0220905.
12. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. Pediatr Blood Cancer. 2007;48: 124-31.
13. Basu S, Saha A, Sarkar S, et al. Clinical profile and therapeutic response of scrub typhus in children: A recent trend from Eastern India. J Trop Pediatr. 2019;65:139-46.
14. Das P, Singh D, Das M, Nayak RK, Mohakud NK. Epidemiological and clinical features of scrub typhus in Odisha, Eastern India. Medical Journal of Dr. DY Patil Vidyapeeth. 2019;12:419-23.
15. Palanivel S, Nedunchelian K, Poovazhagi V, Raghunadan R, Ramachandran P. Clinical profile of scrub typhus in children. Indian J Pediatr. 2012;79:1459-62.

SYSTEMATIC REVIEW

Steroids for the Management of Neonates With Meconium Aspiration Syndrome: *A Systematic Review and Meta-analysis*

TELFORD YEUNG,[1,2] BONNY JASANI[1,2] AND PRAKESH S SHAH[1,3]

From [1] Division of Neonatology, University of Toronto Department of Pediatrics, [2]Hospital for Sick Children, [3]Department of Pediatrics, Mount Sinai Hospital, Toronto, Canada.

Correspondence to: Dr Telford Yeung, Department of Pediatrics, Mount Sinai Hospital, 600 University Avenue, Toronto, ON, M5G 1X5, Canada. telford.yeung@sinaihealth.ca

Background: Steroids are a potential treatment for pulmonary inflammation in meconium aspiration syndrome (MAS). **Objective:** To assess the efficacy and safety of steroids for the management of neonates with MAS. **Design:** Systematic review and meta-analysis of randomized controlled trials (RCT). **Data sources and selection criteria:** A systematic search of PubMed, Embase, Cochrane, and CINAHL was performed from database inception to May 2020 for trials assessing the efficacy of steroids (inhaled/systemic or both) in neonates with MAS. The primary outcome was in-hospital mortality, with secondary outcomes being length of hospital stay and duration of oxygen support. **Results:** Nine RCTs (758 neonates) were included. Overall, steroids did not decrease in-hospital mortality (RR: 0.59; 95% CI 0.28 to 1.23; I^2 = 0%; GRADE: low) nor had any effect on the secondary outcomes. **Conclusion:** There is low quality of evidence that the administration of steroids is not associated with a reduction in mortality in infants with MAS. Further well-designed studies with low bias are needed to draw conclusions.

Keywords: *Dexamethasone, Meconium-stained amniotic fluid, Surfactant, Outcome.*

Meconium aspiration syndrome (MAS) occurs in newborns born through meconium stained amniotic fluid [1]. While in the Vermont Oxford Network, MAS accounted for 1-2% of all NICU admissions with a mortality rate of 2-3% [2]; in India, MAS was the second leading cause of neonatal admissions with mortality ranging between 13% and 32% [3], thus having a substantial impact on hospital expenditure [4]. The current standard of care is supportive therapy with oxygenation and mechanical ventilation [5], with antibiotics and surfactant being common adjunct therapies [5]. For severe cases of MAS, additional interventions include pulmonary vasodilators like inhaled nitric oxide (iNO), vasoactive drug infusions, and extracorporeal membrane oxygenation (ECMO) [5]. Neither antibiotics nor surfactant have shown satisfactory outcomes with respect to mortality in this condition. [6, 7].

The role of steroids in MAS was reported in a systematic review by Cochrane group, in 2003, concluding no benefit of steroids [8-10]. However, this review was limited by a small sample size (85 patients) receiving a suboptimal dose regimen [9,10]. Recent animal studies [11,12] have renewed interest in steroids resulting in several small, single centred randomized controlled trials (RCTs) from resource limited countries where the availability of iNO and ECMO are scarce [13-19]. Therefore, our objective was to systematically review and meta-analyze the efficacy and safety of steroid therapy compared to placebo for infants with MAS. We also intended to assess the type and mode of administration of steroids [13-19].

METHODS

We followed guidelines from the Cochrane Neonatal Review Group [20] for conducting a systematic review and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21] for reporting the results of systematic reviews with meta-analysis. The study was exempted from ethics review.

Search strategy: TY and BJ conducted independent searches of the medical databases namely, Medline, Embase, and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases as well as Cochrane Central Register of Controlled Trials (CENTRAL), without any language restriction, published before May 11, 2020. We also searched first 200 hits of Google Scholar for articles that may not have been indexed in the standard medical databases. The details of the search terms used for the databases and the search output have been shown in **Supp. Table I.**

Search eligibility: Randomized controlled trials studying the efficacy or safety of steroids in newborns with MAS were included. Cross-over studies, systematic reviews

and animal-based studies were excluded. Newborns fulfilling the criteria of late preterm (34+0 to 36+6 weeks gestation), term or post term infants were included. Studies where MAS was diagnosed either by direct aspiration of meconium from below the larynx or respiratory distress within few hours after birth and radiographic features of an aspiration syndrome, were included. The intervention studied was administration of steroids (either inhaled or systemic) in any dose, given within 36 hours of birth, for any duration, for the management of infants diagnosed with MAS compared to no intervention or placebo. The primary outcome for this study was in-hospital mortality. The secondary outcomes were length of hospital stay, duration of oxygen therapy, need for and duration of mechanical ventilation, steroid associated adverse events (hyperglycemia and hypertension) and complications secondary to MAS such as pneumothorax.

After removing duplicates, full texts of potential eligible articles, identified from their abstracts, were obtained and assessed for inclusion.

Data extraction: Two authors (TY, BJ) independently extracted the data using a pre-designed data extraction form. Differences were resolved by consensus or by involving the third author (PS).

Quality Assessment: Assessment was done independently by TY and BJ, using Cochrane collaboration risk of bias (ROB) assessment tool for RCTs [20], which is based on the domains: random number generation, allocation concealment, blinding of intervention and outcome assessors, completeness of follow up, selectivity of reporting and other potential biases. Accordingly, ROB was assigned as low, unclear and high risk. [20].

Statistical analyses: The meta-analysis was performed using RevMan 5 software. Forest plots were calculated using weighted scores and a random effects model (REM, Mantel Haenszel method). We employed REM to account for heterogeneity across studies. Between-studies heterogeneity was assessed with a chi-square test and the I^2 statistic. A *P*-value of < 0.1 for the chi-square statistic indicated significant heterogeneity. For the I^2 statistic, values <25% were considered low heterogeneity, 25-50% moderate heterogeneity, >75% high heterogeneity [20,22]. For studies that presented data as median and interquartile range, we estimated the mean and standard deviation using the minimum and maximum values as well as the interquartile ranges [24]. To combine means and standard deviations, we used calculations provided by the Cochrane handbook [20]. Effect size was reported as relative risk (RR) and associated 95% confidence interval (CI) or mean difference (MD) and 95% CI as appropriate.

Subgroup analysis comparing different modes of administration of steroids: systemic (intravenous) and inhaled steroids vs placebo or no intervention was also performed.

Key information about the study including quality of evidence, details of the intervention and summary of outcome data were included in the summary of findings table according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines. Grading of evidence was performed with the online tool GradePro GDT [23].

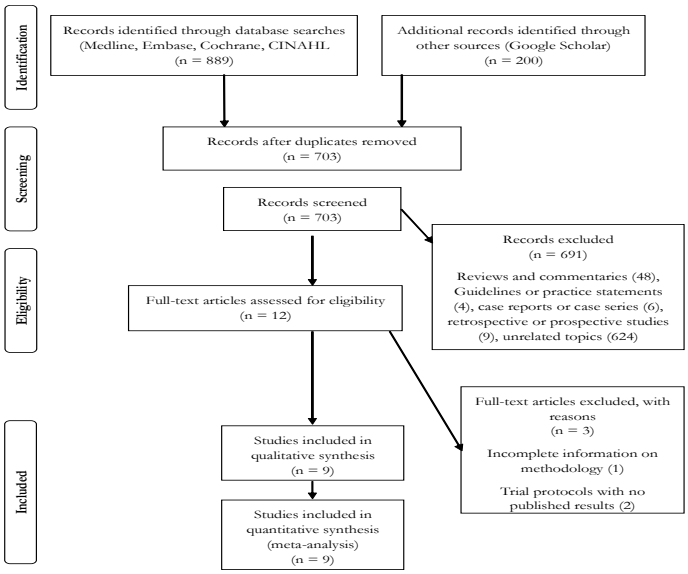


Fig.1 Flow diagram of search strategy and study selection.

RESULTS

A total of nine RCTs, involving 758 newborns were included in this systematic review and meta-analysis (**Fig.1**). The characteristics of the included studies are summarized in **Table I**. Seven RCTs assessed the effects of systemic steroids [9-10,13-14,17-19] while four studies investigated inhaled steroids for MAS [13-16]. Two studies conducted a three arm RCT comparing systemic steroids, inhaled steroids and placebo [13,14]. Among the studies assessing systemic steroids, one used intravenous (IV) hydrocortisone [9], three compared IV methylprednisolone [13-14,19] and three examined IV dexamethasone, in comparison to no intervention or placebo [10,17-18]. Four studies compared the role of inhaled budesonide vs placebo or nebulized saline [13-16].

Using the Cochrane ROB tool, we found that (7/9) 78% of studies had unclear ROB for allocation concealment and (3/9) 33% had unclear ROB for random sequence generation. In the domain of blinding of participants, (5/9) 56% of studies had unclear risk and one study had high risk. For blinding of outcome assessors, 78% of studies had unclear ROB. Detailed quality assessment of the studies is shown in **Supp. Table II.**

Meta-analysis of 7 RCTs (n=423) (**Supp. Fig. 1)** showed no differences in mortality among newborns with MAS treated with steroids compared to the control group [RR (95% CI) 0.59; (0.28, 1.23); P=0.16] [9,10,13-16,18]. The GRADE of evidence was low due to risk of bias and imprecision.

Analysis of duration of hospitalization, reported in 7 studies (642 participants) [10,13-17,19] showed no statistically significant difference between the steroid-treated and control group [MD (95% CI) –2.58 (–5.25,0.08) days; P=0.06] (**Table II**). The duration of oxygen support was also not different between the groups [MD (95% CI) –1.38 (–3.23 to 0.48) days; P=0.15] (**Table II**) [9-10,13-15,18]. Though pneumothorax episodes were decreased, it was not significantly different in the inhaled steroid group compared to control [RR (95% CI) 0.29 (0.06 to 1.38); P=0.12] (**Table II**) [13,15,16]. Regarding mechanical ventilation, while one study assessed the duration of mechanical ventilation [10], the other assessed the need for it [17], thereby making meta-analysis difficult.

The rates of side effects with steroids were not consistently reported. Two trials showed no difference in hyperglycemia between the control and treatment groups during the intervention [RR (95% CI) 1.00 (0.06 to 17.18); P=1.00] (**Table II**) [13,19], and one trial reported no events of hypertension [13].

Subgroup analysis: In subgroup analysis, inhaled budesonide reduced the duration of hospital stay as well as mean duration of oxygen support [13-16] **(Supp. Fig. 2,3)** Similarly, methylprednisolone treated infants showed a significant decrease in duration of oxygen support compared to placebo or no intervention [13-14,18] (**Supp. Fig. 4)**.

Quality of evidence: Using GRADE assessment, the overall quality of evidence for all outcomes was very low to low, due to the high risk of bias, especially selection bias, as allocation concealment and random sequence generation were not reported in the studies. Inconsistency was present as trials used different types of systemic steroids, showing different results. No indirectness was detected. Imprecision was present due to wide confidence intervals. Publication bias was not assessed as we had only 7 RCTs for the primary outcome in this review.

DISCUSSION

In this updated systematic review of 9 RCTs [9,10,13-19], we found that overall, steroids did not significantly decrease mortality in infants with MAS compared to controls. However, inhaled budesonide was found to decrease the duration of hospitalization, while both inhaled budesonide and IV methylprednisolone significantly decreased the duration of oxygen therapy for infants with MAS. Quality of evidence was very low to low due to the small number of trials, high risk of bias and heterogeneity in study interventions.

Animal models of MAS have shown that steroids administered locally or systemically resulted in decreased histologic evidence of pulmonary inflammation and improved oxygenation [11]. Intratracheal steroids decreased neutrophil migration, reduced reactive oxidative damage and subsequently decreased pulmonary tissue necrosis in piglets and rabbits with meconium induced lung injury [11,12]. Thus, there is a biologic plausibility regarding the effect of steroids in neonates with MAS. Even in this review, we identified some positive effects of inhaled budesonide and methylprednisolone in terms of duration of hospital stay and duration of oxygen therapy. Further, inhaled budesonide has the added advantage of avoiding the complications of systemic steroids such as hyperglycemia and hypertension as well as the requirement for IV access, the possibility of infiltration injuries or the risk of IV associated infections. In contrast, Yeh, et al. [9], reported that hydrocortisone increased the duration of oxygen support, which could be explained by differing potency of different steroid compounds. Moreover, methylprednisolone and inhaled budesonide were administered for about seven days, while in the

Table I Characteristics of Included Studies

Study	*Place of study*	*No. of patients*	*Timing and indication for initiating intervention*	*Intervention*	*Control*	*Outcomes*
Systemic steroids compared to placebo						
Yeh, et al. 1977 [9]	Chicago, USA	N = 35 I = 17 C = 18	I = 5.2 (0.4) h C = 4.8 (0.4) h	Hydrocortisone 20 mg/kg IV q12h × 4 doses	Water based diluent with benzyl alcohol	Survival, Duration of oxygen need, Duration of ventilatory support, RDS score, A-aDO2, blood gases
Wu, et al. 1999 [10]	Taipei, Taiwan	N = 50 I = 27 C = 23	Immediately after birth with diagnosis of MAS	Dexamethasone 1.0 mg/kg IV x 1 dose, followed by 0.5 mg/kg IV q12h on day 1-3, the 0.25 mg/kg q12h on day 4-7 for a total of 15 doses	IV saline	Survival, Duration of oxygen need, Duration of ventilatory support, Length of hospitalization
Sangeetha, et al. 2017 [17]	Chidambaram, India	N = 60 I = 30 C = 30	Immediately after birth with diagnosis of MAS	Dexamethasone IV q12h x 7 d (3 d at 0.5 mg/kg followed by 4 d of 0.25 mg/kg)	No intervention	Length of hospitalization, Requirement for ventilation, Occurrence of pneumothorax
Patil, et al. 2018 [18]	Vijayapura, India	N = 70 I = 34 C = 36	After 24-36 h of life with diagnosis of MAS	Dexamethasone IV 0.25 mg/kg q12h x 6 doses starting at 24 or 36 h	No intervention	Length of NICU stay, Oxygen dependence, Occurrence of sepsis, Adverse effects, Feed initiation
Rana, et al. 2018 [19]	Burdwan, India	N = 275 I = 137 C = 138	Within 6 h of birth after diagnosis of MAS	Methylprednisone IV 0.5 mg/kg q12h for 7 days and inhaled budesonide 0.5 mg q12h for 7 d	IV saline + 3% nebulized saline	Need for ventilation, Oxygen dependence, Downes score, Long term complications
Inhaled steroids vs placebo						
Garg, et al. 2016 [15]	New Delhi, India	N = 78 I = 39 C = 39	Within 2 h of birth after diagnosis of MAS	Inhaled budesonide 0.5 mg within 2h and 12 h of life	No intervention	Survival or complications, Length of hospitalization, Length of oxygen need, RDS score
Suresh, et al. 2015 [16]	Mysore, India	N = 40 I = 20 C = 20	After second day of life with diagnosis of MAS	Inhaled budesonide 0.05 mg q12 × 7 d	Nebulized saline	Duration of respiratory distress, Duration of oxygen dependence, Duration of hospitalization, Time to full feeds, Need for mechanical ventilation, Short term complications
Systemic or inhaled steroids compared to placebo						
Basu, et al. 2007 [13]	Varanasi, India	N = 67 I = 34 C = 33	After 24-36 h of life with diagnosis of MAS	Methylprednisolone IV 0.25 mg/kg q12h × 7 d starting after 24 h	Placebo	Duration of oxygen need, duration of ventilatory support, Length of hospitalization, IV fluids requirement, Time to full feeds
Tripathi, et al. 2007 [14]	New Delhi, India	N = 34 I = 17 C = 17	Immediately after birth with diagnosis of MAS	Methylprednisolone IV 0.5 mg/kg q12 × 7 d	IV dextrose 5% and nebulized saline	Length of hospitalization, Survival, O2 dependence, Duration, *X*-ray changes, Sepsis

N: total number of participants; I: number in intervention group; C: number in control group; IV: intravenous; RDS score: respiratory distress score (Downes); A-aDO2: alveolar arterial oxygen gradient; MAS: meconium aspiration syndrome.

Table II Summary of Findings

Outcomes	*No. of participants*	*Relative risk or MD (95% CI)*	*Anticipated absolute effects*		*GRADE*
			Without steroids	*With steroids*	
Steroids vs placebo					
Mortality	423 (7 RCTs)	0.59 (0.28, 1.23)	86 per 1000	51 per 1000	Low[a,c]
Duration of hospitalization (d)	642 (7 RCTs)	–2.58 (–5.28, 0.08)	MD 0 d	MD 2.58 lower (5.25 lower to 0.08 higher)	Very low[a,c,d]
Duration of oxygen therapy (d)	617 (7 RCTs)	–1.38 (–3.23, 0.48)	MD 0 d	MD 1.38 lower (3.23 lower to 0.48 higher)	Very low[a,b,c,d]
Systemic steroids vs placebo					
Mortality	256 (3 RCTs)	0.62 (0.22, 1.73)	71 per 1000	44 per 1000	Very low[a,c,d]
Methylprednisolone vs placebo	101 (2 RCTs)	0.50 (0.12, 2.13)	100 per 1000	50 per 1000	Very low[a,c,d]
Dexamethasone vs placebo	120 (2 RCTs)	0.98 (0.15, 6.41)	34 per 1000	33 per 1000	Very low[a,c,d]
Hydrocortisone vs placebo	35 (1 RCTs)	0.53 (0.05, 5.32)	111 per 1000	59 per 1000	Moderate[c]
Duration of hospitalization (d)	481 (5 RCTs)	–2.74 (–6.68, 1.21)	MD 0 d	2.74 lower (6.68 lower to 1.21 higher)	Low[a,d]
Methylprednisolone vs placebo	371 (3 RCTs)	–4.65 (–9.79, 0.48)	MD 0 d	4.65 lower (9.79 lower to 0.48 higher)	Low[a,d]
Dexamethasone vs placebo	110 (2 RCTs)	–0.39 (–1.01, 0.23)	MD 0 d	0.39 lower (1.01 lower to 0.23 higher)	Low[a,d]
Duration of oxygen therapy (d)	456 (5 RCTs)	–1.16 (–3.83, 1.51)	MD 0 d	1.16 lower (3.83 lower to 1.51 higher)	Very low[a,b,c,d]
Methylprednisolone vs placebo	371 (3 RCTs)	–2.55 (–4.14, -0.95)	MD 0 d	2.55 lower (4.14 lower to 0.95 lower)	Low[a,d]
Dexamethasone vs placebo	50 (1 RCT)	0.40 (–2.43, 3.23)	MD 0 d	0.4 higher (2.43 lower to 3.23 higher)	Moderate[a]
Hydrocortisone vs placebo	35 (1 RCT)	1.35 (1.11, 1.58)	MD 0 d	1.35 higher (1.11 higher to 1.58 higher)	High
Inhaled steroids vs placebo					
Mortality	217 (4 RCTs)	0.55 (0.22, 1.39)	101 per 1000	59 per 1000	Very low[a,c,d]
Duration of hospitalization (d)	208 (3 RCTs)	–4.47 (–8.63, -10.30)	MD 0 d	4.47 lower (8.63 lower to 0.3 lower)	Very low[a,c,d]
Duration of oxygen therapy (d)	208 (3 RCTs)	–2.40 (–3.41, -11.39)	MD 0 d	2.4 lower (3.41 lower to 1.39 lower)	Low[a,d]
Pneumothorax	183 (3 RCTs)	0.29 (0.06, 1.38)	65 per 1000	19 per 1000	Low[a,c]
Hyperglycemia	105 (2 RCTs)	1.00 (0.06, 17.18)	19 per 1000	19 per 1000	Very low[a,c,d]

GRADE- grading of recommendations, assessment, development, and evaluation guidelines. MD-mean difference. [a]Risk of bias due to unclear allocation concealment and inconsistent utilization of random number generator for randomization; [b]Inconsistency due to variation in direction of effect and heterogeneity value >0; [c]Imprecision due to wide confidence intervals; [d]Publication of positive findings from multiple small studies, which may result in omission of negative studies.

study by Yeh, et al. [9], hydrocortisone was administered for two days. The severity of MAS was an important confounding factor, which may explain the observed differences in the effects of the steroid treatments.

Long-term effects of steroids like neurodevelopmental outcomes, could not be assessed in this review due to lack of information. Though two of the studies reported follow-up of patients at 3 or 6 months after therapy [13,19], the method for assessing neurodevelopment was not described in one study [13] and the other described reduction in the composite longterm outcome of bronchopulmonary dysplasia and cerebral palsy [19] without mentioning individual complications.

The limitation of this review is that the included RCTs are small studies with very low to low quality of evidence, due to high risk of bias in different domains. We identified inconsistent reporting of additional outcomes such as duration of non-invasive ventilation, length of mechanical ventilation, use of iNO or need for ECMO, which could be due to the studies being conducted in low- or middle-income countries with limited access to iNO or ECMO. Another limitation is that the degree of severity of MAS varied substantially across studies with mortality ranging between 0-15.7%. The studies did not report the effect of steroids with respect to severity of MAS. Thus, the generalizability of this study to the full spectrum of severity of MAS is limited.

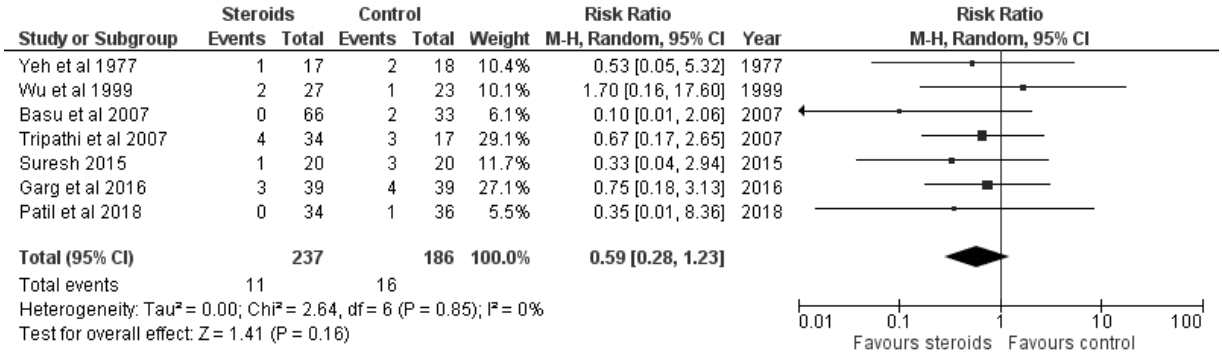
In neonates with meconium aspiration syndrome, low quality evidence suggests that steroid therapy does not reduce mortality. Very low-quality evidence suggests that inhaled budesonide reduces hospital stay while both methylprednisolone and inhaled budesonide reduce the duration of oxygen support. However, number of trials assessing these interventions was small. Further large, multicenter randomized controlled trials assessing the efficacy as well as short- and long-term outcomes of steroids for MAS are needed.

Acknowledgements: Dr Estelle Gauda (Division of Neonatology, Hospital for Sick Children) for her assistance in conceiving this research question and insights into the research topic. Chris Walsh (Sinai Health Systems, Library Services) for his assistance in conducting the literature search.
Funding: None; *Competing interests*: None stated.

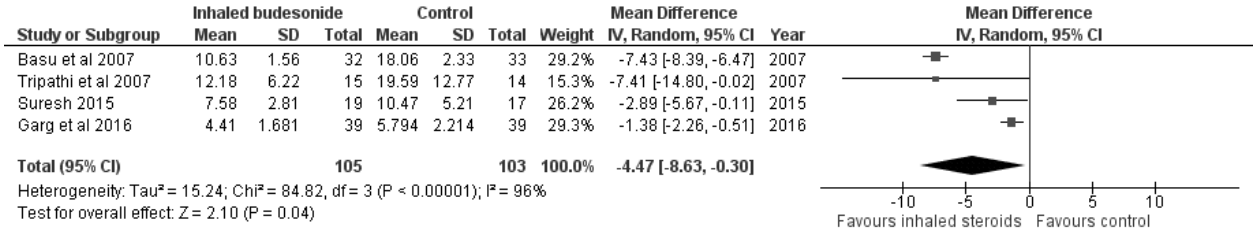
REFERENCES

1. Fanaroff AA. Meconium aspiration syndrome: Historical aspects. J Perinatol. 2008;28:S3.
2. Edwards EM, Lakshminrushimha S, Ehret DE, Horbar JD. NICU admissions for meconium aspiration syndrome before and after neonatal resuscitation program suctioning guideline change. Children 2019;6:1-8.
3. Sivanandan S, Agarwal R, Sethi A. Respiratory distress in term neonates in low-resource settings. Sem Fet Neonat Med. 2017;22:260-66.
4. Thorton PD, Campbell RT, Mogos MF, Klima CS, Parsson J, Strid M. Meconium aspiration syndrome: incidence and outcomes using discharge data. Early Hum Dat. 2018;136:21-26.
5. Chettri S, Bhat BV, Adhisivam B. Current concepts in the management of meconium aspiration syndrome. Indian J Pediatr 2016;83:1125-30.
6. Kelly LE, Shivananda S, Murthy P, Srinivasjois R, Shah PS. Antibiotics for neonates born through meconium-stained amniotic fluid. Cochrane Database of Systematic Reviews 2017;6:CD006183.
7. Natarajan CK, Sankar MJ, Jain K, Agarwal R, Paul VK. Surfactant therapy and antibiotics in neonates with meconium aspiration syndrome: A systematic review and meta-analysis. J Perinatol 2016l36:S49-S54.
8. Ward MC, Sinn JKH. Steroid therapy for meconium aspiration in newborn infants. Cochrane Database of Systematic Reviews. 2003;4:CD003485.
9. Yeh TF, Srinivasan G, Harris V, Pildes RS. Hydrocortisone therapy in meconium aspiration syndrome: a controlled study. J Pediatr. 1977;90:140-43.
10. Wu JM, Yeh TF, Wang JY, et al. The Role of pulmonary inflammation in the development of pulmonary hypertension in newborn with meconium aspiration syndrome. Pediatri Pulm Suppl. 1999;18:205-08.
11. Lin C, Jeng M, Yang Y, Hsiao Y, Kou YR. Comparison of different dosing strategies of intratracheally instilled budesonide on meconium injured piglet lungs. Pediatr Pulmonol 2017;52:891-899.
12. Mokra D, Mokry J, Drgova A, Petraskova M, Bulikova J, Calkovska A. Intratracheally administered corticosteroids improve lung function in meconium-instilled rabbits. J Physiol Pharmacol. 2007;58:389-98.
13. Basu S, Kumar A, Bhatia BD, Satya K, Singh TB. Role of steroids on the clinical course and outcome of meconium aspiration syndrome – A randomized controlled trial. J Trop Pediatr. 2007;53:331-37.
14. Tripathi S, Saili A. The effect of steroids on the clinical course and outcome of neonates with meconium aspiration syndrome. J Trop Pediatr. 2007;53:8-12.
15. Garg N, Choudhary M, Sharma D, Dabi D, Choudhary JS, Choudhary SK. The role of early inhaled budesonide therapy in meconium aspiration in term newborns: A randomized control study. J Matern Fetal Neonatal Med. 2016;29:36-40.
16. Suresh R, Sudha R, Pinto N, Pradeep N. Effect of nebulized budesonide in improving the clinical outcome of neonates with meconium aspiration syndrome. Int J Biol Med Res. 2015;6:4941-45.
17. Sangeetha T, Ramanathan R, Yogavalli S. Effectiveness of steroid therapy in newborns with meconium aspiration syndrome. J Med Sci Clin Res. 2017;5:22587-90.
18. Patil MM, Lakhkar BB, Patil SV. Dexamethasone and outcome of meconium aspiration syndrome: Vijayapur and Karnataka experience. Sri Lanka J Child Health. 2018;47:21-26.

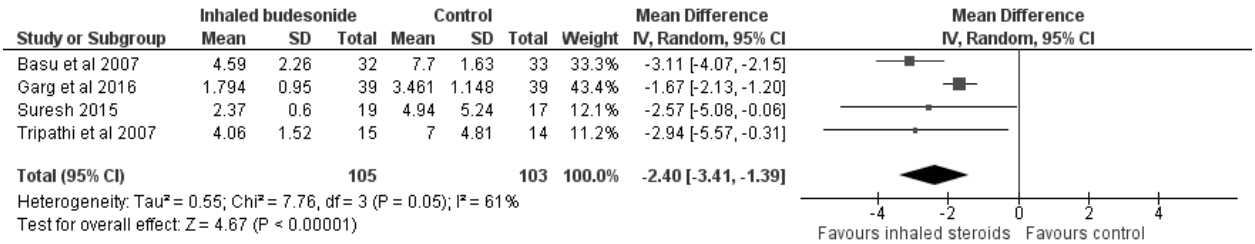
19. Rana KS, Konar MC, Islam K, Barik KL, Nayek K, Datta AK. Study on effects of steroids on clinical course, short-term and long-term outcomes in neonates with meconium aspiration syndrome. J Neonat Nurs. 2018;24:257-60.
20. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Accessed April 14, 2020. Available from *www.handbook.cochrane.org*
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanations and elaboration. BMJ. 2009;339:b2700.
22. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ 2003;327:557-560.
23. Schunemann H, Brozek J, Guyatt G, Oxman A (editors). Guideline Development Tool [updated October 2013]. GRADE working group. Accessed April 23, 2020. Available from *www.gradepro.org*
24. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation form the sample size, median, range and/or interquartile range. BMC Med Res Method. 2014;14:135.
25. Estrany XC. European Clinical Trials Register [Internet]: Amsterdam (Netherlands). Collegi Oficial de Metges de Barcelona (Spain): 2006 – Identifier: 2005-002687-29. Single-dose dexamethasone and/or bronchoalveolar lavage with diluted surfactant in the treatment of severe meconium aspiration syndrome. Accessed May 9, 2020. Available from *https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-002687-29/ES*
26. Rajesh Varma CP. Clinical Trials Register India [Internet]. Swami Dayanand Hospital (India): 2019 – Identifier CTRI/2019/06/019947 Role of budesonide nebulisation in neonates with meconium aspiration syndrome. Accessed May 23, 2020. Available from *http://www.ctri.nic.in/ Clinicaltrials/ pmaindet2.php?trialid=32827*
27. Davey AM, Kueser TJ, Turner HF. Randomized controlled trial of early dexamethasone therapy in the treatment of meconium aspiration syndrome. Pediatr Res. 1995;37:329.



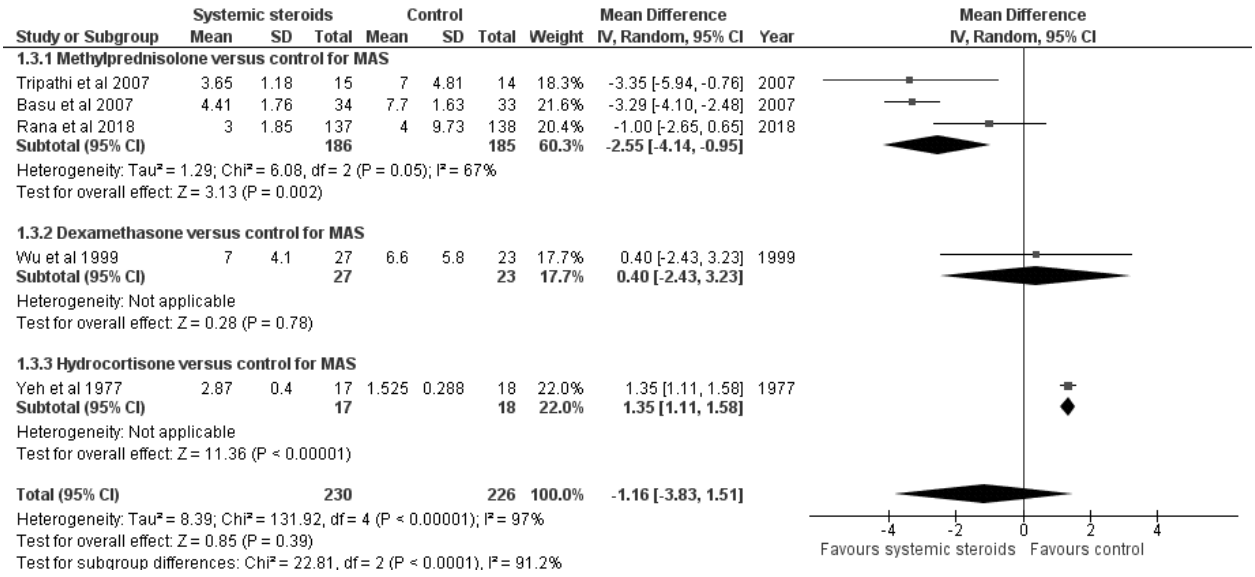
Supplementary Fig. 1 Comparison of in-hospital mortality in infants with meconium aspiration syndrome receiving inhaled steroids versus control.



Supplementary Fig. 2 Duration of hospitalization (days); comparison: Inhaled steroids versus control.



Supplementary Fig. 3 Duration of oxygen support (days); comparison: Inhaled steroids versus control.



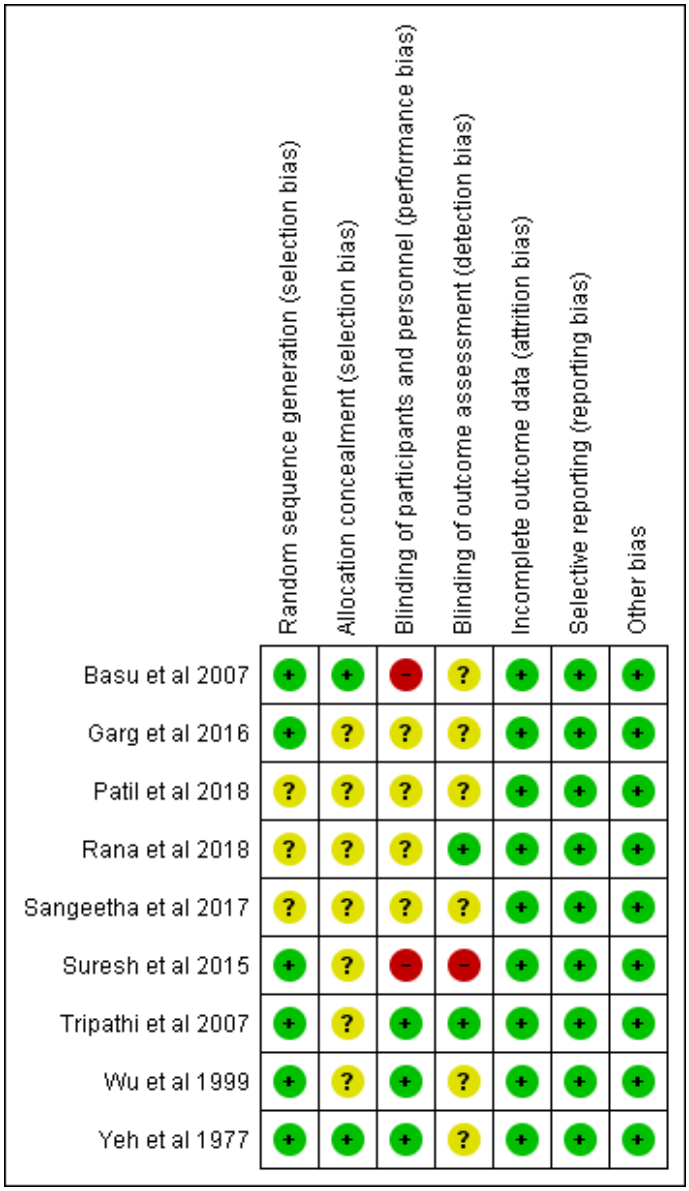
Supplementary Fig. 4 Outcome: Duration of oxygen support (days); Comparison: Systemic steroids versus control

Supplementary Table I Search strategy

Name of Database	Search strategy	Number of articles obtained
Medline	1 Meconium Aspiration Syndrome/ (1085) 2 (meconium adj2 (aspirat* or inhalat* or respirat*)).mp. (1928) 3 (meconium adj2 syndrome*).mp. (1647) 4 exp Steroids/ (851004) 5 exp Methylprednisolone/ (19348) 6 exp Dexamethasone/ (51058) 7 exp Hydrocortisone/ (72791) 8 exp Budesonide/ (4467) 9 steroid*.mp. (330574) 10 methylprednisolone.mp. (26325) 11 Dexamethasone.mp. (71154) 12 hydrocortisone.mp. (76881) 13 budesonide.mp. (6214) 14 1 or 2 or 3 (1998) 15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1073935) 16 14 and 15 (84) 17 Meconium/ (3341) 18 meconium.mp. (7332) 19 14 or 17 or 18 (7332) 20 15 and 19 (259)	**259**
CINAHL	S1 (MH "Meconium Aspiration") S2 (MH "Meconium") S3 TX meconium S4 TX meconium aspirat* S5 TX meconium inhalat* S6 TX meconium syndrome* S7 (MH "Steroids+") S8 TX steroid* S9 (MH "Methylprednisolone") S10 (MH "Dexamethasone") S11 (MH "Hydrocortisone") S12 (MH "Budesonide") S13 TX Methylprednisolone OR Dexamethasone OR Hydrocortisone OR Budesonide S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 S15 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 S16 S14 AND S15 S17 (MH "Hydrocortisone") S18 TX Methylprednisolone OR Dexamethasone	**2**

	OR Hydrocortisone OR Budesonide	
Embase	1 Meconium Aspiration Syndrome/ (1085) 2 (meconium adj2 (aspirat* or inhalat* or respirat*)).mp. (1928) 3 (meconium adj2 syndrome*).mp. (1647) 4 exp Steroids/ (851004) 5 exp Methylprednisolone/ (19348) 6 exp Dexamethasone/ (51058) 7 exp Hydrocortisone/ (72791) 8 exp Budesonide/ (4467) 9 steroid*.mp. (330574) 10 methylprednisolone.mp. (26325) 11 Dexamethasone.mp. (71154) 12 hydrocortisone.mp. (76881) 13 budesonide.mp. (6214) 14 1 or 2 or 3 (1998) 15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1073935) 16 14 and 15 (84) 17 Meconium/ (3341) 18 meconium.mp. (7332) 19 14 or 17 or 18 (7332) 20 15 and 19 (259)	**561**
Cochrane	1 Meconium Aspiration Syndrome/ (1085) 2 (meconium adj2 (aspirat* or inhalat* or respirat*)).mp. (1928) 3 (meconium adj2 syndrome*).mp. (1647) 4 exp Steroids/ (851004) 5 exp Methylprednisolone/ (19348) 6 exp Dexamethasone/ (51058) 7 exp Hydrocortisone/ (72791) 8 exp Budesonide/ (4467) 9 steroid*.mp. (330574) 10 methylprednisolone.mp. (26325) 11 Dexamethasone.mp. (71154) 12 hydrocortisone.mp. (76881) 13 budesonide.mp. (6214) 14 1 or 2 or 3 (1998) 15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1073935) 16 14 and 15 (84) 17 Meconium/ (3341) 18 meconium.mp. (7332) 19 14 or 17 or 18 (7332) 20 15 and 19 (259)	**67**

Supplementary Table II Risk of Bias Assessment



Research for Improving Patient Care

POOJA DEWAN[1] AND HPS SACHDEV[2]

From Department of Pediatrics, [1]University College of Medical Sciences, Delhi; and [2]Department of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi; India.

Correspondence to: Dr. Pooja Dewan, Parsvnath Prestige 2, Sector 93A, Noida, Uttar Pradesh, India. poojadewan@hotmail.com

Research is an integral part of medicine. Health research aims at generating evidence for development of new medicines, procedures and tools, all of which are directed at improved patient care. Research also aims at incorporating this evidence into clinical practice by developing clinical practice guidelines and developing robust health systems including governmental policies and systems. Health research not only allows doctors to decide how to best treat patients but also empowers patients to take active role in their health.

Keywords: *Evidence-based medicine, Health system, Levels of Evidence, Translational medicine*.

Over centuries, health research has relied heavily on keen observation, clinical experience and meticulous planning, all of which has led to evolution of healthcare and innovation in patient care, as is illustrated well by two historical vignettes.

The eighteenth century saw a serendipitous breakthrough in medicine when Edward Jenner, an English physician, discovered the smallpox vaccine based on his observation that milkmaids who developed cowpox were protected from smallpox in due course [1]. Although this was a simple observation, it reiterates the fact that medical science is built out of an eye for detail and a thinking mind.

The importance of structured research including rational use of numbers in medical science can be exemplified by Lind's 'Salisbury experiment' in 1747, largely cited as the first clinical trial [2]. Although, Lind must be commended for using comparable study groups (six therapeutic groups of two participants each) under controlled environment, his observation that oranges and lemons cured scurvy in only one group seems more like a fortuitous discovery. Lind did establish citrus fruits as anti-scorbutic, but his success may simply have been because only one out of the six cures he used had vitamin C whereas the other five did not. Decades later, when lemon juice was unintentionally swapped by lime-juice among sailors on polar explorations, scurvy resurfaced questioning the validity of Lind's trial; for limes contain only half as much vitamin C as lemons and oranges, a fact unknown then.

These examples highlighted that traditional health research, which was largely instinctive, experience-based, riddled with elements of bias, unforeseen errors and confounding variables; needs to be supplanted with robust evidence-based research. Experience-based (non-formal) research can also be misleading and exploitative in the garb of science. The enticing advertisements which manipulate the population beliefs of diet-based or natural remedy-based wellness like supplements to enhance energy and height are clearly logically fallacious and morally repugnant.

While the above examples can be used to scoff at traditional beliefs, the real aim of health research goes much beyond. Health research makes possible the development of new medicines, new procedures and new tools possible which empower the doctors to treat their patients better. Research intends to improve patient outcomes by minimizing error and ensuring a standard of care [3]. Herein, we intend to sensitize the readers to the importance of formal and planned investigations for improving patient care, and how to interpret research.

Types of Health Research

Health research can be categorized as primary or secondary research. Primary research involves conducting studies and collection of raw data by the research team. Secondary research like systematic reviews and meta-analysis involve analysis and synthesis of research conducted by others and could yields results with less cost and sometimes in relatively shorter span of time for the consumption of the readers, although these involve tedious and intense efforts on part of the researcher. Primary health research can be further categorized as basic (bench or laboratory)

research, clinical research and epidemiological research. Basic research includes experimentation in pre-clinical fields such as molecular biology, medical genetics, immunology, animal studies and laboratory research, which provide an understanding into the anatomy, physiology and cellular biology of health and disease, or the biological basis of disease (for example, the effect of copper on oxidative stress in chicken hepatocytes). Clinical research includes interventional studies (clinical trials) or observational studies (cross-sectional, case control, cohort, retrospective, case series), which evaluate disease characteristics, drugs, devices, and diagnostic tools intended for therapeutic, preventive or diagnostic purpose for a disease condition. Examples include: Therapeutic efficacy of intramuscular versus oral vitamin B12 in megaloblastic anemia, association of celiac disease and rickets, and hematological effect of iron supplementation in breast fed term low birth weight infants. Epidemiological studies are population-based (interventional or observational) and aim to identify the cause and distribution of diseases [4]; for example, etiology of pyrexia of unknown origin amongst children from a tribal belt of central India. Health research may also be categorized as qualitative or quantitative [5]. Quantitative research involves direct measurements. Qualitative research is concerned with understanding human behavior from the informant's perspective wherein data are collected by interviews or observation and analyzed by themes derived from participant's description. Research methods can also be categorized as descriptive or analytical.

Choosing a Research Topic: POE Vs DOE

Research should seek to address queries encountered in day-to-day practice. Concerns like morbidity, mortality, or quality of life (for example, oral vitamin D supplementation for reducing severity of pneumonia in under-five children) which matter to both treating physicians and patients are referred to as Patient-Oriented Evidence (POE) or Patient-Oriented Evidence that Matters (POEMs) [6]. Evidence related to incidence, prevalence, etiology, pharmacology, or pathophysiology of disease generate "Disease-Oriented Evidence" (DOE) which are often of greater interest to researchers or laboratory medicine specialists (for example, telomere shortening in leukocytes of children with Human Immunodeficiency Virus).

Research should also focus on the needs of the local population (regionally responsive) and provide solutions which are acceptable, efficacious, safe and sustainable for the region. Most of the low- and middle-income countries (LMICs) could not reap the expected benefits from research conducted or innovations developed in the western countries as the products so developed were either too costly or were not suited to their needs. For example, access to immunotherapy for children with leukemia remains out of reach in most developing countries due to the costs, regulatory barriers, and limited availability of trained health care personnel.

Several pioneering works by Indian physicians can serve as role models for integrating research into office practice and offer need-based solutions in the Indian and other LMIC contexts. Starting from the mid-twentieth century, Dr. Chatterjee can be credited for publishing the first paper on use of oral rehydrating therapy for cholera in humans [7]. Subsequently, contributory efforts of Indian clinicians [8-10] established the therapeutic role of oral zinc in acute diarrhea in under-five children, which has since been adopted by WHO as a standard of care alongside oral rehydration solution. Establishing room air as the modality of choice for resuscitating asphyxiated neonates has been another pioneering work [11]. The development of Rotavac®, a low-cost indigenous rotavirus vaccine is also a noteworthy innovation [12]. Some other researchers helped shape the guidelines for management of regional public health problems like rickettsial illness [13], and scorpion envenomation [14], and unfold the mystery behind hypoglycemic encephalopathy which was perplexing for the physicians in Western Uttar Pradesh [15]. All these indigenous research works and many more are embodiment of the quote "With every lock comes a key".

Planning Research: Methods and Designs

Depending upon the research question, a particular research method may be more suited. For example, questions about people's perceptions of COVID-19 illness may be answered by qualitative research, but the efficacy of a drug like Remdesvir in the treatment of severe COVID-19 illness are better enunciated through a clinical trial or a case-control design. All these research methods are generally used to complement each other in order to understand a phenomenon as completely, as feasible. **Fig. 1** summarizes the various types of research designs that can be employed.

Evidence-based Medicine (EBM)

Clinical decisions backed by scientific evidence inspire confidence and conviction to the clinician. Levels of evidence (LOE) are assigned to studies based on the methodological rigor of their design, validity, and relevance to patient care. These levels are arranged in a hierarchical fashion to depict an Evidence Pyramid [16]. The studies like the systematic reviews and meta-analysis

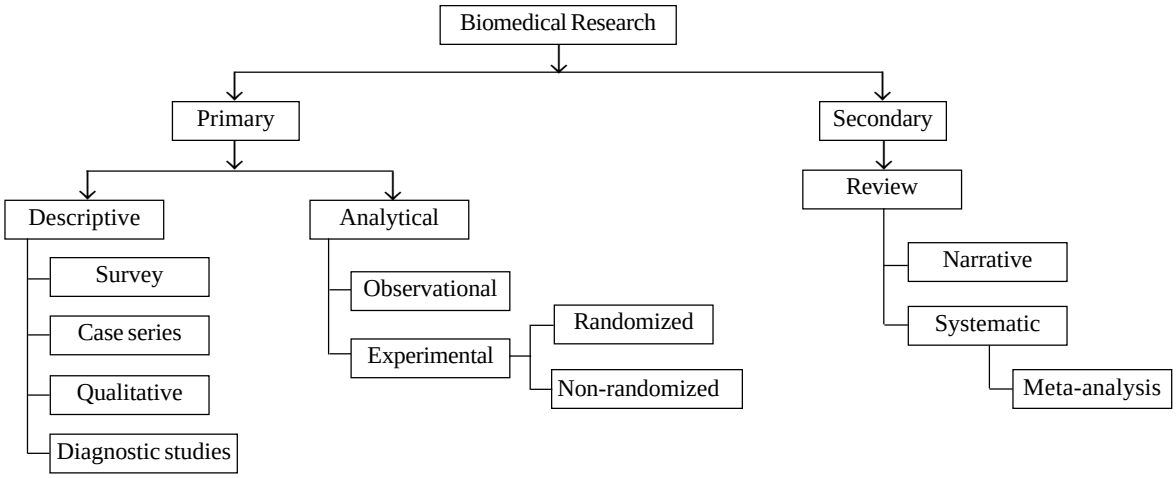


Fig. 1 Study designs and methods used in biomedical research.

or homogenous randomized controlled trials (RCTs), are regarded as the highest quality and are placed at the apex of the pyramid (Level 1 evidence). Observational research is lower and expert opinion is at the lowest rung (Level 5 evidence) as depicted in **Fig. 2**. The type of available evidence is dependent upon the research question and may not always be the highest level of evidence. Some studies would be deemed unethical for RCT design; for example, randomizing newborn infants to receive breastfeeding or a formula feed for determining effect on body composition. In such situations, it is best to work the way down the Evidence Pyramid to the next highest level of evidence.

Scrutiny of Evidence

RCTs are the often allocated the highest level of evidence, however, their respective results should be carefully scrutinized with respect to their power, bias or other types of errors. For example, an underpowered RCT on vitamin D supplementation for decreasing severity of pneumonia in under-five children may yield a negative result when in fact vitamin D supplementation could be beneficial. The assessment criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [17], may be used to help ascertain the methodological rigor of a RCT; factors like sequence generation (selection bias), absence of allocation sequence concealment (selection

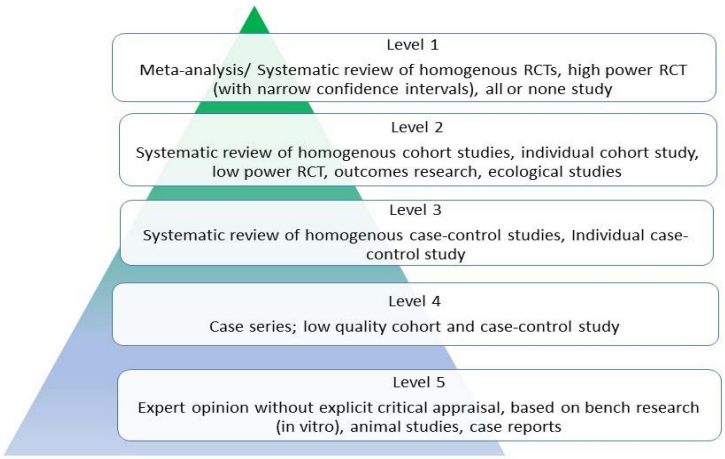


Fig. 2 Hierarchy of study designs and levels of clinical evidence.

bias), lack of blinding of participants and personnel (performance bias), not blinding the assessors of outcome (detection bias), missing outcome data (attrition bias) and selective reporting or deliberate suppression of outcome (reporting bias) need consideration. Presence of these biases undermines the confidence in interpretation and conclusions. Likewise, for observational studies, confounding variables and bias need to be ascertained using the detailed Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [18].

Grading of Evidence

It is important for a clinician to not only keep abreast of the latest research but also be aware of limitations of the studies. Hence, a grading system (grades A, B, C and D) is in place to assist the clinician for decision-making and adopting evidence into practice [19]. This grading takes into account the research question, the available scientific evidence including their methodological rigors and limitations like imprecision, inconsistency, indirectness of study results, and publication bias. It does not downgrade lower level evidence when deciding recommendations provided the results are consistent. For example, a strong recommendation (grade A) is given to both level I evidence as well as consistent evidence from Levels II, III and IV studies. Consistent level 2 or 3 studies and extrapolation from level 1 studies are given grade B. Level 4 studies and extrapolation from level 2 or 3 studies are allotted grade C. Level 5 evidence and inconsistent or inconclusive studies from any level are the lowest grade (grade D).

Bringing Published Research into Practice

It is important to critically evaluate published research before adopting it into practice. While it is good to consider the methodological rigor of published data, yet what gets published is not always sacrosanct. Journals often publish only a small fraction of the studies while most of the studies with negative results (i.e., those failing to yield statistical significance*)* remain in closets and drawers. Publication bias, predatory editorial practices, and ritualistic statistical practices can all be counterproductive to EBM. Clinical practice decisions should not be based on a single study. Clinical decisions based on low-quality evidence can unintentionally lead to alarming consequences for the patient. Considerations of cost, regional applicability (similarity between your health set up and the study setting), and benefits of change compared to the risks, and legal implications should be considered in addition to the merits of study design and its results. Although "to err is human", it is unacceptable that health care system should end up harming the patients whom it is designed to protect.

Responsible Conduct of Research in Minors

Children are a vulnerable group with their own specific needs and hence research needs to be focused to address their unique issues. Research in children is also challenging as these young participants need to be specially protected while we seek answers to clinical questions and issues which can offer them benefit. Growth, development and childhood illnesses are research areas which are well recognized in this group. Alongside, focused research on neonatal health and disease and adolescent health are also addressed by including these specific cohorts as research participants. However, children should be research participants only if the research question can be answered by their participation. Research should always be conducted in adults before children unless the disease is unique to pediatric age group like Kawasaki disease, birth asphyxia, neuroblastoma, congenital adrenal hyperplasia, etc. Likewise, issues pertaining to neonates like interventions for neonatal resuscitation can only be addressed by studying neonates in research. It is important to remember that findings of research on adults should not be extrapolated to children. For example, dose of a particular drug (established in adults) in a child weighting one-half of the adult weight cannot be simply axed to half! However, despite the need for pediatric research, it has been a low priority at policy level. Ethical constraints (limited ability of the child to understand the implications of research, coercion, guardianship and autonomy of the child), lack of funding, and reluctance by community are some major impediments to research in children. Consequently, recommendations in children are often derived from adult studies or no studies at all!

Translational Medicine: Bench to Bedside

Evidence-informed practice is critical to delivery of optimum healthcare. Any lag in the translation of research into practice can lead to overuse, underuse, and misuse of evidence [20]. Overuse refers to the continued use of ineffective interventions or interventions with a scope for greater harm than advantage; for example, empirical use of antibiotics in all preterm neonates admitted to the intensive care unit. Failure to provide treatment despite robust scientific evidence would constitute underuse; for example, failure to prescribe zinc supplements for acute dehydrating diarrhea in toddlers. Misuse would occur when the prescribed treatment is neither apt nor safe leading to adverse health effects; for example, routine prescription of oral steroids in all wheezy children. Translational medicine aims at bridging this 'Know-Do gap' by incorporating evidence-based findings into office practice in a timely manner. Translational researchers use

KEY MESSAGES

- Research should be relevant, participatory, and patient-oriented.
- A critical appraisal of the research methodology and its validation is imperative before translating the findings into routine clinical practice.
- Evidence-based medicine, translational medicine and health systems research are the triology of biomedical research.

secondary research methods to scale up the application of scientific evidence to the level of the healthcare system rather than the individual healthcare providers.

Implementation Science: Challenges and the Road Ahead!

Implementation science is the "scientific study of methods to promote the systematic uptake of evidence-based research into routine practice, and, hence, to improve the quality and effectiveness of health services and care" [21]. Development of clinical practice guidelines (CPGs) and their dissemination is one of the most tactical methods to translate evidence into practice. However, it is important to consider that mere publication of CPGs cannot ensure change in clinical practice. Simultaneous publication of overlapping guidelines by different scientific bodies, rapidly emerging scientific evidence rendering the existing guidelines redundant (for example, therapeutic use of hydroxychloroquine in COVID-19), trust in the validity of current practice methods, contradictory information from different information sources, lack of awareness among practicing physicians, personal bias of the physicians based on experience, and poor health systems constitute major barriers to implementation of CPGs into practice. Numerous obstacles can impede conduct of clinical trials in LMICs like the lack of infrastructure, heterogeneity of resource availability among countries, unfamiliarity with clinical trial regulations, cultural/ethical issues, and other legal constraints around data-sharing. Only about 10% of the global expenditure on health research and development was used for research in the developing countries where 90% of all preventable global deaths had occurred [22]. A mere 0.09% of the gross domestic product (GDP) in India was spent on health research in 2011-12 and only a meager 0.02% was available from public sources [23].

Despite evidence to show that patients treated at research-active hospitals fare better [24,25], many hospitals have not been able to completely integrate research into clinical care across all their specialties. Mistrust in health systems and fear of being exploited prevents patients from participating in research. Lack of financial incentives, miniscule funding for research, no protected time for research, high expectations of patients, societal norms, complacency of physicians developed through years of traditional practice, fear of litigation hassles, cumbersome patent laws, and ethical and regulatory clearances, deter most practicing doctors from participation in research.

To foster improvement in health research, it is imperative to understand the magnitude of the 'Know-do gap' at the level of providers and institutions, and augment the dissemination of evidence from health research, infrastructure, funding and priority-setting for health research. The setting up of Department of Health Research (DHR) by the Ministry of Health and Family Welfare in 2007 has been a welcome step to this effect. Innovation in the medical education system coupled with greater use of digital technology in research as well as healthcare delivery are needed. E-medicine or telemedicine can aid healthcare delivery. A change in the attitudes of healthcare providers and patients is also needed wherein patients are treated as clients. Patients need to participate not only in their own healthcare decisions but also in research through informed consent. A more participatory role of the patients and an overall positive outlook of the clinicians to be involved in research will ensure a more robust health system in the future.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Smith KA. Edward Jenner and the small pox vaccine. Front Immunol. 2011;2:21.
2. Hughes RE. James Lind and the cure of scurvy: An experimental approach. Med Hist. 1975;19:342-51.
3. Krzyzanowska MK, Kaplan R, Sullivan R. How may clinical research improve healthcare outcomes? Ann Oncol. 2011;22 Suppl 7:vii10-vii15.
4. Röhrig B, du Prel JB, Wachtlin D, et al. Types of study in medical research: Part 3 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2009;106:262-8.
5. Lakshman M, Sinha L, Biswas M, et al. Quantitative vs qualitative research methods. Indian J Pediatr. 2000; 67:369-77.

6. Smith R. A POEM a week for the BMJ. BMJ. 2002; 325:983.
7. Chatterjee HN. Therapy of diarrhoea in cholera. Lancet. 1953;265:1045-6.
8. Sachdev HP, Mittal NK, Mittal SK, et al. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr. 1988;7: 877-81.
9. Bhatnagar S, Bahl R, Sharma PK, et al. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: A randomized controlled trial. J Pediatr Gastroenterol Nutr. 2004;38:34-40.
10. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6 to 35 month old children with acute diarrhea. J Pediatr. 2002;141:677-82.
11. Ramji S, Rasaily R, Mishra P, et al. Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: A multicentric clinical trial. Indian Pediatr. 2003; 40:510-17.
12. Ella R, Bobba R, Muralidhar S, et al. A Phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India. Hum Vaccin Immunother. 2018;14:1791-1799.
13. Rathi NB, Rathi AN, Goodman MH, et al. Rickettsial diseases in central India: Proposed clinical scoring system for early detection of spotted fever. Indian Pediatr. 2011;48:867-72.
14. Vashishtha VM, Kumar A, John TJ, et al. Cassia occidental is poisoning causes fatal coma in children in western Uttar Pradesh. Indian Pediatr. 2007;44:522-5.
15. Kale AA. A crusade against scorpion sting: Life and works of Dr. Himmatrao Bawaskar. J Family Med Prim Care. 2012;1:52-5.
16. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009). Accessed on October 31, 2020. Available from: *https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.*
17. Higgins JPT, Thomas J, Chandler J, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Accessed November 1, 2020. Available from: http://*www.training.cochrane.org/handbook.*
18. Sterne JAC, Higgins JPT, Elbers RG, et al and the development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): Detailed guidance, updated 12 October 2016. Available from: *http://www.riskofbias.info.* Accessed October 26, 2020.
19. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3 rating the quality of evidence. J Clin Epidemiol. 2011;64:401-6.
20. Institute of Medicine. Crossing the quality chasm: A new health system for the 21st century. 2001. Accessed October 30, 2020. Available at: *http://www.nationalacademies.org/hmd/w/media/Files/ Report%20Files/2001/Crossing-the-Quality-Chasm/Quality%20Chasm%202001%20%20report%20brief. pdf*
21. Eccles MP, Mittmann BS. Welcome to implementation science. Implem Sci. 2006;1:1.
22. Kilama WL. The 10/90 gap in sub-Saharan Africa: Resolving inequities in health research. Acta Trop. 2009;112:S8-S15.
23. Dandona L, Dandona R, Kumar GA, et al. Mapping of health research funding in India. Natl Med J India. 2017;30:309-16.
24. Downing A, Morris EJ, Corrigan N, et al. High hospital research participation and improved colorectal cancer survival outcomes: A population-based study. Gut. 2017;66:89-96.
25. Nijjar SK, D'Amico MI, Wimalaweera NA, et al. Participation in clinical trials improves outcomes in women's health: A systematic review and meta-analysis. BJOG. 2017;124:863-71.

IAP Guideline on Practicing Safely During COVID-19 Era: Clinics and Small Establishments

GV BASAVARAJA,[1] SUPRAJA CHANDRASEKAR,[2] ARUN BANSAL,[3] DHIREN GUPTA,[4] BAKUL JAYANT PAREKH,[5] SS KAMATH,[6] SNEHAL DESAI,[7] PRITESH NAGAR,[8] NITIN SHAH,[9] ATANU BHADRA[10] AND AJ CHITKARA[11] FOR INDIAN ACADEMY OF PEDIATRICS

From [1]Paediatric Intensive Care Unit, Indira Gandhi Institute of Child Health, Bangluru, Karnataka; [2]Columbia Asia Referral Hospital, Yeshwanthpur, Bengaluru; [3]Division of Pediatric Critical Care, Department of Paediatrics, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh; [4]Pediatric Intensive Care Unit, Sir Ganga Ram Hospital, New Delhi; [5]President (2020), Indian Academy of Pediatrics; [6]Department of Pediatrics, Indira Gandhi Cooperative Hospital, Ernakulum, Kerala;[7] Amruta Hospital, Surat, Gujarat; [8]Consultant Pediatric Intensivist, Hyderabad, Telangana; [9]Department of Pediatrics, PD Hinduja Hospital, Mumbai, Maharashtra; [10]ESI Hospital, Asansol, West Bengal; and [11]Department of Pediatrics, Max Superspeciality Hospital, Shalimar Bagh, New Delhi; India.

Correspondence to: Dr Arun Bansal, Professor, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. drarunbansal@gmail.com

Justification: The unprecedented COVID-19 pandemic has had a formidable impact on Indian health care. With no sight of its end as yet, various establishments including the smaller clinics and nursing homes are restarting full operations. Hence, there is the need for recommendations to allow safe practice ensuring the safety of both the heath care worker (HCW) and patients. **Process:** Indian Academy of Pediatrics organized an online meeting of subject experts on 27 July, 2020. A committee was formed comprising of pediatricians, pediatric and neonatal intensivists, and hospital administrators. The committee held deliberations (online and via emails) and a final consensus was reached by November, 2020. **Objectives:** To develop recommendations to provide a safe and practical healthcare facility at clinics and small establishments during COVID times. **Recommendations:** The key recommendation to practise safely in this setting are enumerated. Firstly, organizing the out-patient department (OPD). Secondly, appropriate personal protective equipment (PPE) to provide protection to the individual. Thirdly, decontamination/disinfection of various common surfaces and equipment to prevent transmission of infection from fomites. Next, maintaining the heating ventilation and air conditioning (HVAC) to provide a stress-free, comfortable, and safe environment for patients and HCWs. Finally, steps to effectively manage COVID-19 exposures in a non-COVID-19 facility. All these measures will ensure safe practice during these unprecedent times in clinics and smaller establishments.

Keywords: *Preparedness, Physical distancing, Resource-limited setting, SARI*.

The healthcare industry not only bears the brunt of the coronavirus disease (COVID-19) epidemic, but has also to mitigate its spread too. In this regard, putting strict practices and processes in place that are suitable to the local needs and resources will be paramount in fighting this disease effectively.

The Indian Academy of Paediatrics (IAP) has therefore come out with the following guidelines on practicing safely in clinics and small establishments during these unprecedented times.

OBJECTIVES

To develop recommendations to provide a safe and practical health care facility at clinics and small establishments during COVID times, and to ensure safety of the healthcare workers (HCW), and patients at clinics and small establishments.

PROCESS

The Indian Academy of Pediatrics organized an online meeting of subject experts on 27 July, 2020. A committee was formed comprising of pediatricians, pediatric and neonatal intensivists, and hospital administrators. The committee held various deliberations (online and via emails) and a final consensus was reached by November, 2020.

RECOMMENDATIONS

The guidelines are applicable for clinics, polyclinics, and level 1 hospitals.

A clinic is defined as a clinical establishment providing examination, consultation, and prescription to outpatients, including dispensing medicines by a single doctor, general practitioner, specialist, or a super-specialist doctor. A polyclinic is similar but managed by more than one doctor,

general practitioner, specialist, or a super-specialist doctor. [2] A Level 1 (A) hospital is a general medical service with an indoor admission facility, provided by recognized allopathic medical graduate(s) and may also include general dentistry services offered by recognized BDS graduates. Example: Primary Health Care Centre (PHC), government and private hospitals, and nursing homes run by MBBS doctors. A Level 1 (B) hospital shall include all the general medical services provided at level 1(A) and indoor and OPD specialist medical services provided by doctors from one or more basic specialties, namely general medicine, general surgery, pediatrics, obstetrics and gynecology, and dentistry. [3]

The guideline will be discussed under these broad subheadings

- Organising the Out Patient Department [OPD]
- Personal Protective Equipment (PPE) and Innovation
- Sanitisation Recommendations
- Heating Ventilation and Air Conditioning [HVAC]
- Protocol for post-Covid-19 exposure in a Non-Covid-19 zone

Organizing The Outpatient Department

1. *Staff Skills Training and Education* - The first step in organizing the OPD is the education of HCW on PPE, disease transmission, screening techniques, cohorting patients, and newer clinic management protocols. [4] The clinician should be prepared for HCW's illness & subsequent quarantine by training the staff to multitask and alternating their duties. [5] In the Indian scenario, with constraints in the availability of skilled staff, prevention is the key.

2. *Tele Consultation* - With the legalization of teleconsultations, it is recommended wherever feasible. [6] It helps to identify patients who can be managed at home and those who need hospital care. It minimizes patient contact and is a useful triaging tool. The teleconsultation guidelines laid down by the government need to be followed [7].

3. *Appointments and Patient Scheduling* - Limit the number of patients per day. Walk-In consultations should be discouraged to avoid overcrowding. Patient segregation & triaging to be done while scheduling appointments [6].

4. *Physical Distancing and Waiting Areas* - Clinics should preferably have no waiting areas. However, when more than one person arrives, their seats should be at least 1 meter apart. [5,6] Open ventilation is encouraged here [refer section on HVAC]. In single room OPD chambers, it would be prudent to call one patient at a time; others can wait outside in the open air or their vehicles.

5. *Patient Segregation* - It is prudent to cohort children who are ill from the well-baby visits. Many clinics are operated only by the practicing doctor. However, it is recommended to have a helper who will assist in triaging, maintaining decorum, and educating patients. Preferably an initial screening should be followed by separation of those suspected of COVID-19 from others. These cases should not spend time in the waiting area and should be seen immediately. A separate entry, consultation place & exit, if feasible, will help. [4] As not all clinics have the facilities mentioned above, alternate precautions should be followed:

- Telephonic triaging and schedule appointments for all suspect cases *after* routine OPD [6]
- Exclusive days should be allotted for 'Well baby' & Immunization checks once or twice a week. This may even boost parents' morale who otherwise would be scared to come to clinics for vaccinations.

6. *Patient Education and Awareness* - All patients should follow respiratory hygiene and cough etiquette. Patients should be provided with tissues, contactless bins, contactless sanitizers, and wash areas. Display these instructions in prominent locations. Patient education is also the physician's responsibility, hence putting educative posters, multimedia information at strategic points is useful. [4,6]

7. *One Attendant and Personal Protection* - Allow only one parent or guardian with the child. [5] Everybody, including children above two years, should wear a mask.

8. *Well Ventilated* - Follow the ventilation guidelines provided in this document.

9. *Avoid Fomites* - Remove toys, magazines, and any items that are likely to be shared between patients in the waiting area or consultation chambers. [4]

10. *Novel Techniques* - Innovative methods have been tried by various doctors and can be utilized.

- Using transparent physical barriers between the patient and doctors can help in decreasing direct exposure to droplets.
- Virtual detailed video interaction followed by a rapid, focused examination of the patient in another chamber minimizes the patient contact time.
- Non-Contact Thermal scanners- These are convenient non-contact devices ideally suited for mass screening in a pandemic and have wide acceptability. However, they lack robust evidence. A recent systematic review

showed reasonable diagnostic accuracy in fever detection but may vary with patient characteristics, setting, index test, and the reference standard used. These have an excellent negative predictive value. [9] However, there are more recent studies doubting its accuracy during screening in a pandemic. [10] Hence, no specific recommendations are available for or against the use of these devices.

Personal Protective Equipment [11]

PPE, along with other measures like engineering and administrative protocols, reduces the exposure of HCW to infectious agents, including the SARV-CoV2 virus. *HCW has 11-fold higher chances of getting infected* with the SARS-CoV2 virus than the general population. The use of PPE can reduce that risk by 60-80% when exposed to COVID-19 suspected or proven cases. Various components of PPE and its benefits are given in **Supplementary Table I**.

Donning and Doffing PPE

An essential part of PPE is the proper way of putting it on (Donning) and removing (Doffing) as the maximum chances of contamination and infection occur during doffing. The steps and sequence of donning and doffing of N-95 masks and PPE are given in **Supplementary Table II**. All PPE components, especially face masks are effective only when used in combination with frequent hand hygiene.

Type of exposure and use of PPE for HCW

Every patient should be taken as a COVID-19 suspect unless proven otherwise. Appropriate PPE should be universally worn when attending to any patient, even in a non-COVID-19 centre.

- In non-aerosol generation areas - head cap, face mask, goggles, and gloves.
- For aerosol generation areas and procedures - In addition, wear body gowns, shoe cover, and face shield.
- While attending a proven COVID-19 patient - Full Hazmat suit PPE.
- Nonmedical staff not in direct contact with patients - triple-layer surgical masks and gloves inside the clinic. They must maintain physical distancing and frequently use hand hygiene.

Patient PPE

- All patients and their attendants should wear a mask.
- Using a triple layer surgical mask or N-95, if possible, significantly reduces the risk of transmission.

Adjuncts to PPE

- Patients often complain that the doctor is not audible with PPE. One adjunct is to use a wireless or wired mini personal voice amplifier
- The use of the mobile phone is inevitable but often results in the breach of PPE. Hence, using a blue tooth device, preferably with bone conduction that doesn't plug the ear, is advised.
- Rexene covers or disposable paper covers/sheets for the patient sitting/lying areas.
- Contactless/foot operated dispensers for soap/ sanitizer/water in washbasins.

Sanitization Recommendations

Despite consistent evidence of contamination of various surfaces with SARS CoV 2 virus, especially in the hospital setting, there is no direct evidence of fomites being a cause of transmission. [12] However, it is imperative to follow some necessary sanitization precautions for the decontamination/disinfection of COVID-19, as given in **Table I**. These are based on the Hospital Infection Prevention and Control guidelines drafted by the National Centre for Disease Control and the WHO. [13]

Spraying and Fogging

Spraying, fogging, misting, or fumigation of rooms or surfaces is not recommended for COVID-19. Spraying of chemicals is harmful, affecting the mucus membrane, skin, and respiratory system. The recommended method is to wipe with a disinfectant soaked cloth

Hand Hygiene

Patients, attendants, and HCW's are advised to wash hands with soap and water in a washbasin with foot-operated or motion sensor adapted taps. Everyone should use Foot-operated hand sanitizer dispensers before entering the clinic.

Sanitizers

The composition of sanitizers is 60-70% ethanol or isopropyl alcohol. Avoid methanol containing or non-alcohol based sanitizers. Foot operated and Contactless sanitizer delivery systems are safe and effective.

Heating ventilation and air conditioning (HVAC)

Maintaining the HVAC plays a vital role in providing a stress-free, comfortable, and safe environment for patients and health care workers. Maintaining indoor air quality is very important to prevent cross-contamination and hospital-acquired infections.

Table I Decontamination and Disinfection Guide

Area	*Item/Equipment*	*Process*	*Procedure*
General area	Dust Mop	Sweeping	• Dust/Wet mop to remove surface dust • No broom • Remove gathered dust with hearth brush & shovel
Clinical areas and waiting rooms	Three buckets each with Hot Water Detergent 1% NaClO[a]	Cleaning & Mopping	- Prepare a detergent solution with warm water - Mop with detergent water, allow dry, clean mop with plain water, squeeze dry, then mop with NaCLO; Mop twice a day - In areas where there is a spill-using a spill kit, first, discard the sharps in the sharps bin, then cover any spills with 1% NaCLO for 10-20 min contact, then wipe and follow the above standard cleaning process
Ceiling and walls	- Dusting tool with a long handle - soap solution - Plain water	Damp dusting	Damp dusting with very little moisture, just enough to collect the dust.Done in straight lines that overlap one another. Once weekly
	Care of Mop - Clean with hot water and detergent solution, disinfect it with sodium hypochlorite and keep for drying upside down		
Doors and doorknobs	Damp sponge Detergent Water	Thorough Washing	- Frequently touched surfaces – cleaned daily
Stethoscope	ABR[b]/Spirit swab	Cleaning	- Disinfection before every patient contact - Cleaning with detergent & water or 70 % Isopropyl Alcohol or 2 % bleach solution (may cause discoloration) Do not use Hand sanitizers-(due to harmful additives), Do not use any sterilization process, never immerse it in any liquids
BP cuffs and covers	Detergent Hot water	Washing	- Disinfect covering by wiping with ABR, Regular washing of the cover
Thermometer	ABR	Cleaning	- Prefer one thermometer per patient - Disinfect with ABR between every patient
Injection and dressing trolley	Detergent and water Duster Disinfectant (70% Alcohol)	Cleaning	To be cleaned daily with detergent and water. After each use should be wiped with disinfectant.
Refrigerators	Detergent and water Absorbent cloth	Cleaning (weekly)	Defrost, decontaminate, and clean with detergent.
Furniture and fittings	Warm water and detergent, cloth	Dusting	Using warm water and detergent, damp dust all furniture & fittings;
Curtains	Soft clothes Water, Mild soap solution	Cleaning	Clean with water and soap for curtains
Soap dispensers and water jars	Detergent and water	Daily dusting	Soap dispensers- Should be cleaned weekly with detergent and water and dried. Water jars after cleaning as above, water to be boiled and cleaned before refilling
Cleaning of toilets	Sodium hypochlorite 1% Soap powder Long handle angular brush Nylon scrubber	Cleaning	Scrub with soap solution, wash with water, then sterilize with NaCLO 1% for floors and commode. For taps, sink, and commode accessories, use only soap and water.
Drying the floors with a separate drying mop should be done			

[a]NaClO = Sodium hypochlorite, [b]ABR=Alcohol based rub.

Importance of HVAC in the context of COVID 19

1) The SARS (Severe Acute Respiratory Distress Syndrome) epidemic in the past has taught us that there was an increased rate of intrahospital spread of infection, and it was attributed to architectural factors and HVAC systems. The SARS-CoV2 virus is resistant to various temperatures. Unfortunately, people are switching off air conditioning [AC] facilities to curb the spread. However, this is ineffective and, in fact, harmful as it creates adverse working conditions.

2) It is a misconception that if we maintain moderate humidity, the virus growth and propagation can be prevented. Unfortunately, this virus seems to be very resistant to environmental changes like temperature and humidity. It requires an extreme relative humidity of more than 80 percent and a temperature of more than 50 degrees Centigrade to control. These conditions are neither attainable nor acceptable. [14]

Air changes per hour (ACR)

Air changes per hour (ACR) are the number of total replacements of any room's air in one hour. If the air supply by the HVAC system in one hour is equal to the volume of the space, then it is called one air change per hour. The number of air exchanges required to clean the air depends on the quantum of infected aerosol production. For example, *a minimum of 12 ACR is needed in the Intensive Care Unit (ICU). In contrast, only 4 ACR is required for general wards*, as the expected amount of aerosol production is different in both areas.

There are two ways to reduce the quantum of infection in contaminated air, either by 'diluting' the pathogen *(dilution ventilation)* or by removing the pathogen *(exhaust ventilation)*. Dilution Ventilation is also called *positive pressure isolation*, required to prevent infection in an immunocompromised patient. Exhaust Ventilation is called *negative pressure isolation* and is used primarily to avoid a contaminated patient's airborne disease [15] (**Fig. 1**).

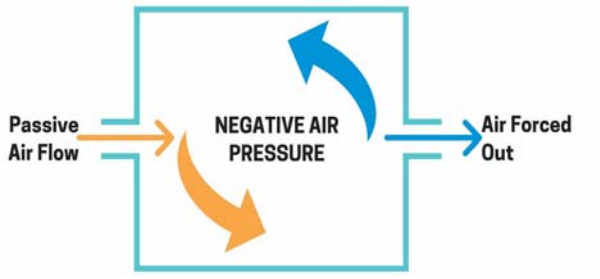


Fig. 1 Principle of HVAC to prevent airborne spread.

Ways To Create Air Exchanges Via Exhaust Ventilation:

1) *Cross Ventilation* by opening up doors and windows: This is the cheapest way, but by this method, we cannot control the thermal and pollution level.

2) *Exhaust Fan:* The exhaust fan creates a negative pressure in the room, which sucks the dirty and contaminated air out of the room, and fresh air is pulled to replace it.

3) *Fully Controlled Air:* Air inlet, as well as exhaust air, is fully controlled, including the temperature and filtration. This requires a lot of resources, including technology, and is best suited for negative pressure isolation wards and ICUs.

4) *Air Purifying Systems:* This cleans the air either via filtration (e.g., HEPA) or via other techniques like ultraviolet rays. Recirculation of air has to be prevented for this system to be effective.

The airflow should be in the direction of clean to dirty and should not be directed towards the patient as it causes turbulence. (**Fig. 2**)

Plasma Purifiers

Plasma purifiers are specialized newer technology air purifiers. Originally these purifiers were very large and cumbersome, however, with significant advancements in technology, they have become compact and a part of the

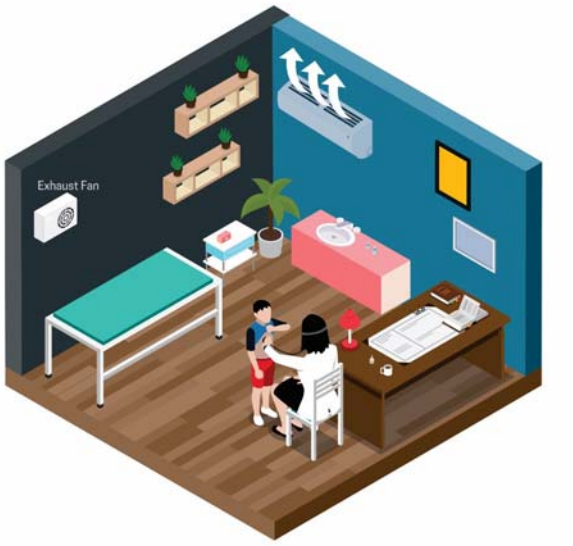


Fig. 2 Clinic setting - Placement of exhaust fan, one feet above the ground. Direction of air should be from clean to dirty (patient side). Flow of AC air should be directed towards celling.

HVAC with the ionization tubes mounted in the air conditioning, either in the unit itself or in the ductwork. These ionization tubes form ions (negatively or positively charged particles) as air circulates over them. The ions that are produced act in three ways to purify the air:

1) *Sterilize bacteria and mould*. When bacteria, virus and spores of mould come in contact with the ions, they are oxidized and destroyed. They can no longer multiply and are eliminated from the air.

2) *Reduce particles in the air.* The ions produced by the system bond with the toxins in the air, causing these particles to become larger. That makes them easier to be capture in the filters, reducing the number of toxin particles in the air.

3) *Control odors*. Odors associated with household aerosols or cleaning products are "captured" by the ions, oxidized, and eliminated.

The viricidal properties of the Plasma purifiers may be used while installing the HAVAC in the clinics and small establishments. However further evidence is required regarding its efficacy during this pandemic.

Recommended HVAC Modifications For Healthcare Facilities:

Different recommendations for HVAC for various healthcare facilities are given in **Supplementary Table III** and **Figs. 1,2 & 3**.

Covid-19 Exposure In A Non-Covid Health Facility

There are various situations where a Non-COVID-19 facility is faced with a COVID- 19 challenge. The possible problems and recommendations are enumerated.

When patients admitted for unrelated/non-respiratory illness turn out to be COVID-19 positive

1. Inform the local health authorities
2. Assign anyone dedicated HCW, wearing a full PPE, to attend to this case
3. The patient should be shifted to a separate designated isolation area.
4. Arrange for transfer to a COVID-19 isolation facility after due communication
5. Follow appropriate standard precautions while transporting the patient
6. Followed by disinfection procedures at the facility and the ambulance
7. All contacts (see below) should be identified, risk assessment is done and subsequently follow the testing and quarantine recommendations.
8. All high-risk contacts should be put on Hydroxychloroquine [HCQ] chemoprophylaxis for seven weeks, keeping in mind the contraindications of HCQ.

HCW turn out to be positive for COVID-19 [16]

1. HCWs developing respiratory symptoms (e.g., fever, cough, shortness of breath) should be considered a suspected case of COVID-19.
2. Should immediately inform his supervisor.
3. Should be isolated, and arrangements must be made to refer to a COVID-19 designated hospital (if not already working in such a facility) for isolation and further management. However, asymptomatic, and mildly symptomatic HCW's need to be home isolated under supervision.
4. Should be immediately taken off the roster
5. All health facilities must have a staffing plan in place for such an event to maintain continuity of operations
6. Ensure that the disinfection procedures are strictly followed

The decision on further /continued use of non-COVID-19 facilities where a single/multiple

COVID-19 case has been reported [16]

1. If the hospital authorities are reasonably satisfied that the source case/s have been identified and isolated, all contacts have been traced and quarantined, and adequate disinfection has been achieved, the hospital will continue to function.
2. In addition to the steps taken above, if the health facility continues to report new hospital-acquired COVID-19 cases in the following days, it would be advisable to temporarily close the health facility's defined section where the maximum number of patients are being reported.
3. After thorough cleaning and disinfection, it can be put to use again.
4. Local guidelines for the region should be followed

Standard Operating Procedure to be followed in case HCW reports exposure/breach of PPE [17]

1. All the HCW must report every exposure to COVID-19 to the concerned nodal officer and Head of the concerned department immediately

Definition of Contacts

A *contact* is a person who is likely to get the infection from a positive case through any of the following modes of transmission

- Anyone exposed to a COVID -19 positive case 2 days before and 14 days after the onset of symptoms or date of testing
- The duration (>15 minutes) and proximity (< 1meter) of exposure and the use of appropriate PPE during exposure are an important consideration in defining the contact

Primary /High-Risk Contact

- Anyone with proximity within a 1-meter distance of the confirmed case
- Anyone who touched or cleaned the linens, clothes, utensils of the patient
- Had direct physical contact with the patient including examination or touched the body secretions including blood saliva, urine, etc. without appropriate PPE
- Anyone who has come in contact with aerosol-generating procedures is considered to be high-risk contact

Secondary/Low-Risk contact

- Any contact not fitting into the above description
- Low-Risk contacts also can be spreaders of infection hence need monitoring

Risk Assessment

The risk assessment of close contacts with COVID-19 patients is given in **Table II**.

Recommendations for Monitoring Based on COVID-19 Exposure Risk [17]

High- and Medium-risk Exposure Category

- HCW in the high- or medium-risk category should undergo active monitoring, including restriction from work in any healthcare setting until seven days after their last exposure. [18]
- High-risk contacts will be quarantined for seven days
- Test for COVID-19 done on day 0 of exposure and if negative day 7 of exposure
- If they test positive but are asymptomatic, they will follow the protocol for mild/pre-symptomatic cases
- If they test negative and are asymptomatic, they should complete a 7-day quarantine from the last date of exposure and then return to work. Further, they should be in self-reporting observation at work for another minimum of 7 days and strictly abide by the mask and physical distancing rules.
- If they develop a fever (measured temperature > 100F or subjective fever) OR respiratory symptoms consistent with COVID-19 (e.g., cough, shortness of breath, sore throat), they should immediately test and self-isolate and notify the senior staff to take further action.

Low-risk Exposure Category

- HCW in the low-risk category should perform self-monitoring with delegated supervision until 14 days after the last potential exposure.
- Asymptomatic HCW in this category are not restricted from work.
- They should check their temperature twice daily and remain alert for respiratory symptoms consistent with COVID-19 (e.g., cough, shortness of breath, sore throat)
- Test for COVID-19 between day 5 and 14 of exposure
- Suppose they develop a fever (measured temperature > 100F or subjective fever) OR respiratory symptoms. In that case, they should immediately self-isolate (separate themselves from others) and notify the staff

Table II Risk Assessment of Close Contacts

Prolonged close contact with a COVID-19 patient who was not wearing a facemask (i.e., no source control)	
Epidemiological Risk Factor	Risk
HCP PPE: None	High
HCP PPE: Not wearing a surgical facemask or N95 mask	High
HCP PPE: Not wearing eye protection	Medium
HCP PPE: Not wearing a gown or gloves	Low
HCP PPE: Wearing all recommended PPE (except wearing a surgical facemask instead of an N95 mask)	Low
Prolonged close contact with a COVID-19patient who was wearing a facemask (i.e., source control	
Epidemiological Risk Factor	Risk
HCP PPE: None	Medium
HCP PPE: Not wearing a surgical facemask or N95 mask	Medium
HCP PPE: Not wearing eye protection	Low
HCP PPE: Not wearing a gown or gloves	Low
HCP PPE: Wearing all recommended PPE	Low

HCP – Healthcare professional; PPE – Personal protective equipment.

physician promptly so that they can coordinate consultation and referral to a healthcare provider for further evaluation.

Disclaimer: This practice guideline is intended to assist pediatricians and their support staff in safely practicing during the COVID-19 pandemic. The guideline at best serves as a quick reference providing practical advice on continuing medical practice in a safe way in clinics and small establishments. This is a broad advisory and is not intended to override any local or national government policies. This guideline is based on the currently available evidence on COVID-19 and its applicability in the Indian context. With any further developments, the guideline will be subjected to change.

Contributors: SC, DG, AB, GVB: conception and design of the work and drafting the work; BJP, SSK, SD, PN, NS, AB, AJC: substantial contributions to the acquisition and interpretation of data for the work, and revising it critically for important intellectual content. All authors provided approval for the final version to be published.

Funding: None; *Competing Interests*: None stated.

REFERENCES

1. Clinical Establishment Act Standards for Clinic / Polyclinic with Dispensary CEA /Clinic- 009 Accessed November 8, 2020. Available from *http://clinicalestablishments.gov.in/WriteReadData/5541.pdf*
2. Clinical Establishment Act Standards for Hospital (LEVEL 1A &1B))/ CEA/Hospital – 001. Accessed November 8, 2020. Available from: *http://clinicalestablishments.gov.in/WriteReadData/147.pdf*
3. American Academy of Family Physicians. Checklist to Prepare Physician Offices for COVID-19. Accessed July 28, 2020. Available from *https://www.aafp.org/dam/AAFP/documents/patient_care/publichealth/COVID-19%20Office%20Prep%20Checklist. pdf*
4. Centers for Disease Control. Healthcare Facilities: Get Your Clinic for Corona Virus 2019 (Covid-19). Published March 11, 2020. Accessed July 28, 2020. Available from *https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinic-preparedness.html*
5. Indian Academy of Pediatrics. Covid-19 Bulletin 2nd Edition. Accessed July 28, 2020. Available from *https://iapindia.org/pdf/Final-Edited-Version-of-IAP-COVID19-Bulletin.pdf*
6. Ministry of Health and Family Welfare. Telemedicine Practice Guidelines. Published March 25, 2020. Accessed August 1, 2020. Available from *https://www.mohfw.gov.in/pdf/Telemedicine.pdf*
7. Indian Academy of Pediatrics. COVID-19 Bulletin 2nd Edition. Accessed July 28, 2020. Available from *https://iapindia.org/pdf/Final-Edited-Version-of-IAP-COVID19-Bulletin.pdf*
8. Aggarwal N, Garg M, Dwarakanathan V, et al. Diagnostic accuracy of non-contact infrared thermometers and thermal scanners: A systematic review and meta-analysis. J Travel Med. 2020;27:taaa193.
9. Khan S, Saultr, B, Adams S, et al. Comparative accuracy testing of non-contact infrared thermometers and temporal artery thermometers in an adult hospital setting. Am J Infect Control. 2020; S0196-6553(20)30892-0. [Epub ahead of print]
10. Guidelines on rational use of personal protective equipment. Ministry of Health and Family Welfare Directorate General of Health Services [Emergency Medical Relief]. Accessed October 25, 2020. Available from*https://www.mohfw.gov.in/pdf/GuidelinesonrationaluseofPersonalProtectiveEquipment.pdf*
11. National Guidelines for Infection Prevention and Control in Healthcare Facilities, Ministry of Health and Family Welfare Directorate General of Health Services, Government of India. Accessed October 25, 2020. *https://ncdc.gov.in/index1.php?lang=1&level=1&sublinkid=692&lid=546.*
12. World health Organization, Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific Brief. Accessed October 24, 2020. Available from *https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions*
13. How to operate air conditioning and ventilation systems to control the spread of coronavirus disease (COVID-19) in Residences, Workspaces, and Healthcare Facilities: IMA HBI-Indian Society of Heating, Refrigerating & Air Conditioning Engineers COVID-19 GUIDANCE DOCUMENT. Accessed August 11, 2020. Available from *https://ishrae.in/mailer/ISHRAE_COVID-19_Guidelines.pdf*
14. World health Organization, Natural Ventilation for Infection Control in Health-Care Settings: Edited by Atkinson J, Chartier Y, Lúcia Pessoa-Silva C, Jensen P, Yuguo Li, Wing-Hong. Accessed August 11, 2020. Available from *https://www.who.int/water_sanitation_health /publications /natural _ventilation*
15. Interim United States Guidance for Risk Assessment and Work Restrictions for Healthcare Personnel with Potential Exposure to COVID-19. Accessed October 25, 2020. Available from *hhttps://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html*
16. Guidelines to be followed on detection of suspect/confirmed COVID-19 case in a non COVID Health Facility. Ministry of Health & Family Welfare Directorate General of Health Services Emergency Medical Relief Division. Accessed October 25, 2020. Available from *https://www.mohfw.gov.in/pdf/GuidelinestobefollowedondetectionofsuspectorconfirmedCOVID19case.pdf*
17. Revised quarantine and testing protocol for primary/high risk contacts and secondary/low risk contacts. Commissionerate Health & Family Welfare Services, Government of Karnataka 15-09-20, No DD/SSU/Circular-06/2020-21.

Annexure I

Members of National Expert Committee

Dr Bakul Jayant Parekh, President IAP 2020, Dr Basavaraja G - Chairperson; Prof Arun Bansal – Coordinator; Dr Dhiren Gupta – Convenor; Dr Supraja Chandrasekar, Dr SS Kamath, Dr Snehal Desai, Dr Pritesh Nagar, Dr Nitin Shah, Dr Atanu Bhadra, Dr AJ Chitkara.

Supplementary Table I Various Components of Personal Protective Equipment and Their Use

Type of PPE	*Use*	*Comments*
Head cap: 	Covering for hair & scalp which is not readily washable every time Use where aerosol generation /close patient contact	Disposable- SMS* material or hood of Hazmat suit or reusable cloth
Goggles: 	Fitted eye protection, worn over spectacles, avoid when using a face shield Use where aerosol generation /close patient contact	Sanitise with soap solution/ ABR #& reuse
Face shield 	Cover the ear lines on both sides and crown to chin vertically Use where aerosol generation /close patient contact	Disposable ones -transparent sheet on a head ring or sturdy reusable, reliable polycarbonate helmets For intubation goggles preferred Sanitize like the goggles
Shoe covers 	Used in Covid wards	Disposable shoe cover for feet or leggings that go up to the knees.
Surgical Gloves: 	Need not change the gloves after each patient, sanitize adequately between two patients. Discard when any minute cuts or breach on the gloves Use double gloves and discard the outer one after examining suspected patients	Latex or more sturdy and hypoallergic Nitrile ones

Body gowns:  	Recommended when seeing a suspect or proven case. It can be worn as a routine to protect one's clothing. For limited exposure [like routine examination], use a Surgical cloth gown with a disposable plastic sheet over the gown (Like used in HIV set up). Disposable SMS gowns are light, breathable, and comfortable. Innovative Gowns - reusable cloth gowns with plastic layer sewn over the cloth in front 2/3rds and entirely around the sleeves - used for moderate risk of exposure [body fluid splashing expected]. High-risk exposures like while working in COVID19 proven areas or in Operating Theatres must wear Hazmat suits that provide 360-degree protection.	Gowns can be cloth surgical gowns, disposable SMS gowns, or overalls. Aprons - not recommended. Surgical gowns prevent gross contamination of personal clothes are insufficient to prevent infection as they are water-permeable Reusable bodysuits that can be autoclaved or chemically sterilised for a limited number of uses.
Triple-layer pleated surgical mask 	Use genuine brands Masks prevent droplet infection or a splash of fluids. Do not let the mask hanging from the neck. Change mask after 6 hours or as soon as they become wet. Surgical masks, if worn tightly, can show resistance while exhaling, similar to N95 masks. These masks are disposable and are never to be reused. Do not use masks with valves/filters.	Donning- First sanitize hands; unfold the pleats; make sure that they are facing down in front of the mask. Place over nose, mouth, and chin. Fit flexible nose piece over nose bridge and tighten the nose clip adequately. Secure with tie strings, upper string on top of the head above ears, and lower string at the neck's back. Ensure no gaps, adjust to fit. Doffing- remove from behind (without touching the front of the mask). First, untie the string below and then the string above and handle the mask using the upper string. Dispose of in a yellow waste bag. Sanitize hands

Respirators/N95/FFP2 masks:   	These masks fit tightly on the face leading to an effective seal and, hence, efficient for HCW in clinics. They come in a cup shape, D shape, or duckbill shapes. Do not use any respirator mask with an exhalation valve N99, N100, FFP3, P3 reusable respirators filter 99-99.9% of 0.3-micron size particle or larger. These are expensive and are not required except in the high-risk zone like operation theatre.	Use only certified genuine respirators, like certified by NIOSH, USA, or FFP2 $ approved by the European certifying Committee (CEN). Genuine N95 masks can be identified by having words NIOSH certified' and 'TC number' printed on the mask. One can verify the manufacturer from the NIOSH website. Do not touch the N95 mask once worn. If touched, sanitize Never keep the mask hanging below the nose or chin. Use an N95 respirator for a maximum of 8 hours Don't reuse N-95 respirator after accidental contamination with blood or body fluids.
Donning: Sanitize hands. Do not allow facial hair, clothing, or anything else to prevent proper seal between the face and the respirator. Position the respirator in hand with the nose piece at your fingertips. Cup the respirator in your hand, allowing the headbands to hang below your hand. Hold the respirator under your chin with the nosepiece up. While wearing, first wear the lower strap over your neck and then the upper strap over your ears/head. Tighten the straps adequately as required for the leak test. The top strap rests at the top back of your head. The bottom is positioned around the neck and below the ears. Do not crisscross. Leak test: After wearing an N95 mask, do a proper fit and a leak test. Place both hands over the respirator, take a quick breath in to check whether the respirator seals tightly to the face. Place both hands completely over the respirator and exhale. If you feel leakage, there is not a proper seal. If air leaks around the nose, readjust the nosepiece clip. If air leaks at the mask edges, readjust the straps along the sides of your head until a proper seal is achieved. When you inhale sharply after a properly fitting mask, the mask tip should suck in a bit towards your face. Doffing: Sanitize your hands. Remove the lower strap and leave it in front hanging. Next, remove the upper strap and remove the mask without touching the front part of the mask. Hold the mask from the sides where the straps are attached and put it in a paper bag for future use or dispose of in a yellow waste bag.		

*-SMS - Spunbound Meltblown Spunbound, #- ABR – Alcohol Based Rub, $ FFP Filtering Face Piece

Supplementary Table II Steps and Sequence to Wear an *N*-95 Mask and PPE

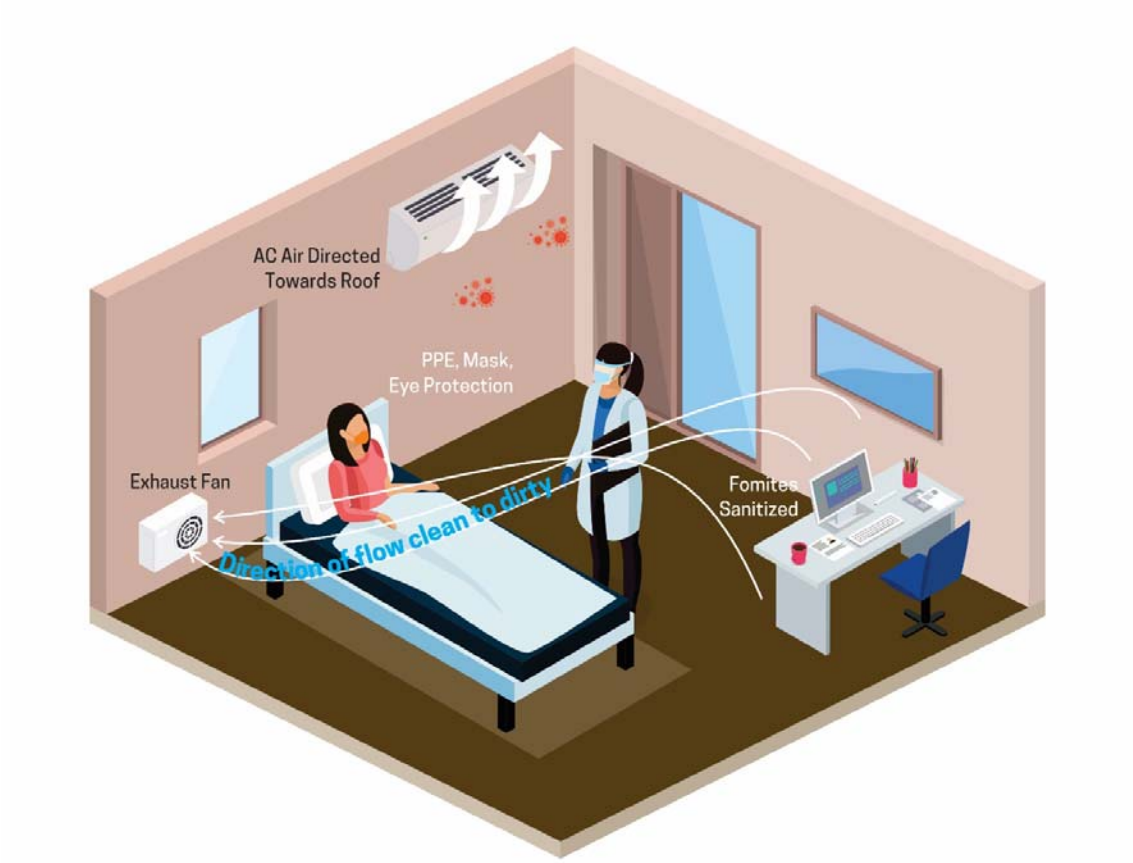
Donning of Mask	*Leak test*	*Doffing of Mask*
Sanitize your hands	After wearing the N-95 mask, do a proper fit and a leak test.	Sanitize your hands.
Do not allow facial hair, clothing, or anything else to prevent proper seal between the face and the respirator	Place both hands over the respirator, take a quick breath in to check whether the respirator seals tightly to the face.	Remove the lower strap and leave it in front hanging.
Position the respirator in hand with the nose piece at your fingertips.	Place both hands completely over the respirator and exhale. If you feel leakage, there is not a proper seal.	Next, remove the upper strap and remove the mask without touching the front part of the mask.
Cup the respirator in your hand, allowing the headbands to hang below your hand.	If air leaks around the nose, readjust the nosepiece clip.	Hold the mask from the sides where the straps are attached and put it in a paper bag for future use or dispose of in a yellow waste bag
Hold the respirator under your chin with the nosepiece up.	If air leaks at the mask edges, readjust the straps along the sides of your head until a proper seal is achieved.	
While wearing, first wear the lower strap over your neck and then the upper strap over your ears/head.	When you inhale sharply after a properly fitting mask, the mask tip should suck in a bit towards your face.	
Tighten the straps adequately as required for the leak test. The top strap rests at the top back of your head.		
The bottom is positioned around the neck and below the ears		
Do not crisscross		
PPE Donning Sequence		**PPE Doffing Sequence**
Hand hygiene		Outer glove
Cap		Gown
Shoe cover		Shoe cover
Hand hygiene		Goggles/ Face shield
Inner glove		Mask
Gown cover all		Cap
Mask [Three ply/N95]		Inner glove
Goggles/Face shield		Hand hygiene

Supplementary Table III Humidification Ventilation and Air Conditioning Modifications for Healthcare Facilities

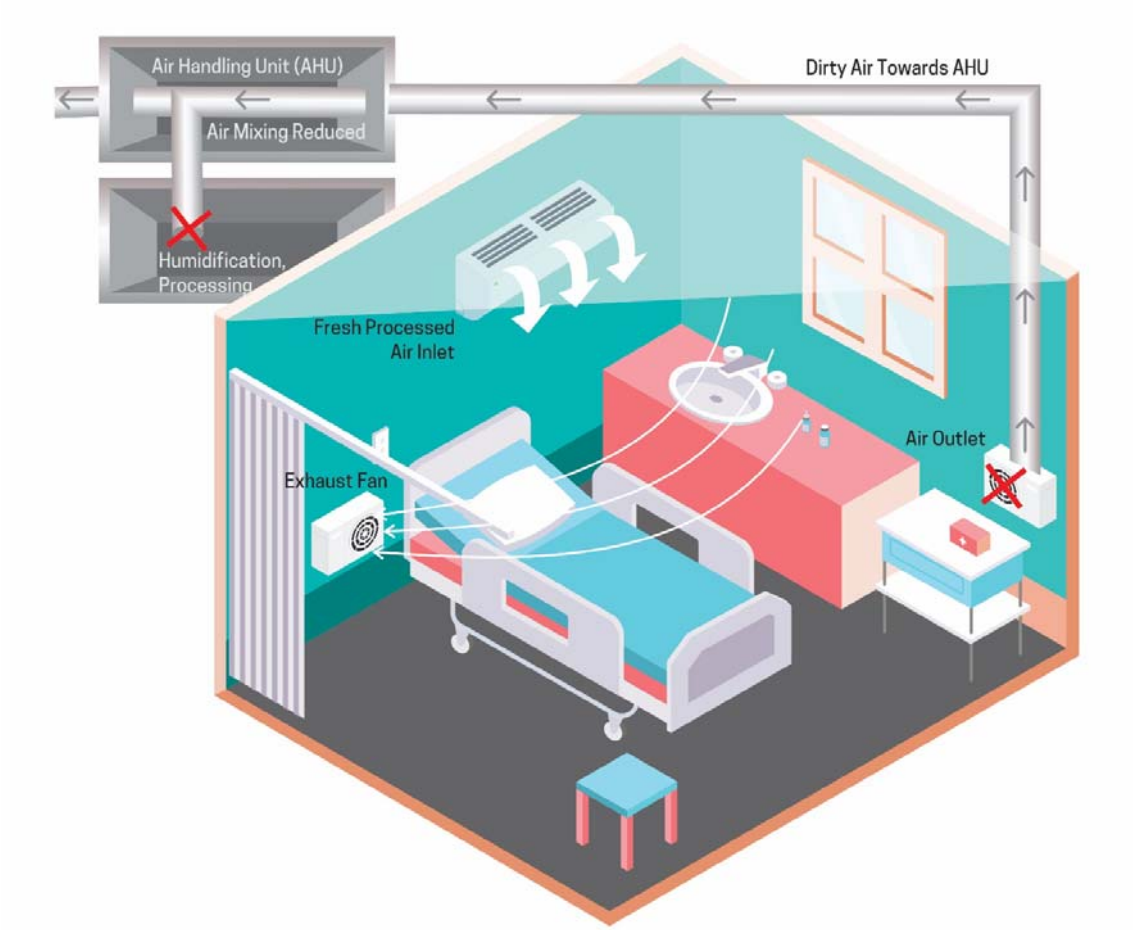
Health Care Facility	*HVAC Modification*	*Remarks*
Single room clinics (see figure 2)	1) Install exhaust fan 12 inches above floor towards the patient end with windows sealed.	In case an adjacent washroom is available with an installed exhaust fan, the fan should be switched on; it may require increasing the strength for making it useful.
	2) Air conditioner temperature should be set to provide comfort to occupants. May require increasing the cooling strength or install one more AC	• Draft of air from AC* or cooler should not be directed towards occupants • Air exhaustion can compromise the cooling of the clinic.
	3) If the installation of an exhaust fan not possible, then a medical-grade air purifier can be used	The selection of air purifiers should be based on the size of the room. The HEPA # filter should be a grade of 13 plus or MERV 17 plus. Air Purifier, on its own, is inferior to exhaustion of air.
	4) Droplets based ultraviolet C rays sanitation (cleaning of floor and walls) methods are of limited use. Air sterilization methods require sophisticated equipment with high radiation strength and are expensive	There should be a gap of at least 7 feet between occupants and UVC$ irradiation. UVC (254 nm wavelength) irradiation with an exposure time of 15 minutes at an irradiation intensity of 4016 μW/Cm2 resulted in complete inactivation of SARS-CoV ǂ
2) Clinic without facilities of air cooler, air conditioners, exhaust fan.	Improve cross-ventilation by opening doors and windows.	Opening windows and doors increases air exchange per hour to more than 8. However, it compromises the quality of air and can lead to thermal stress Difficult to tolerate PPE ^ in uncontrolled temperature
3) Polyclinic – Multiple rooms	Placement of PVC** ducts with exhaust fans (see figure 3)	Air should be exhausted safely. Care to be taken not to exhaust air to other occupied areas.
4) Conversion of an emergency room in the isolation	Natural ventilation – open door and windows – permit cross ventilation	Air temperature should be monitored to avoid thermal stress.
	Anteroom available – Place exhaust fan in the washroom and convert	

room	anteroom to the positive pressure room Anteroom not available – Place inline exhaust fan (figure 7)	
5) Conversion of ICU in the temporary isolation room. (figure 5,6,7)	1)Placement of PVC ducts with exhaust fans (see figure 3). PVC ducts should be placed above the false ceiling, and all inlets which transfer the air from contaminated area to the air handling unit should be sealed. AHU## should be provided fresh air as much as technically possible. 2) Place HEPA based air purifier (figure 4)	1)Decontaminate air by applying HEPA filter or exhaust 3 meters above the highest point of the building 2) Intake of HEPA filter should be from fresh source as well as air should be exhausted out of room to prevent recirculation 3) Room doors and windows should be sealed for 5 PSI negative pressure to be created. 4)Minimum of 12 air exchanges to be produced 4) Use Maghelic pressure gauze or Smoke/tissue to ascertain effective negative pressure.
Exhaust fan capacity selection	As per the size and air exchanges required	CFM $$ = Volume of the room x Air changes desired per hour/ 60 (Minutes)
Selection of HEPA filters	1) Medical grade 2) HEPA 13 plus (Particle size less than 0.3 microns) clearance by 99.7 efficiency or MERV value 17 plus (Hyper HEPA filters)	The HEPA filter on its own is not effective in preventing spread, prevention of recirculation of the contaminated air
Example - Calculation of air exchange per hour for selecting air purifier based on HEPA filter Room Volume= 15X15X8.5 =1913 cubic feet 150 CFM X 60 minutes /1913 Cf = approx. 5 ACH		

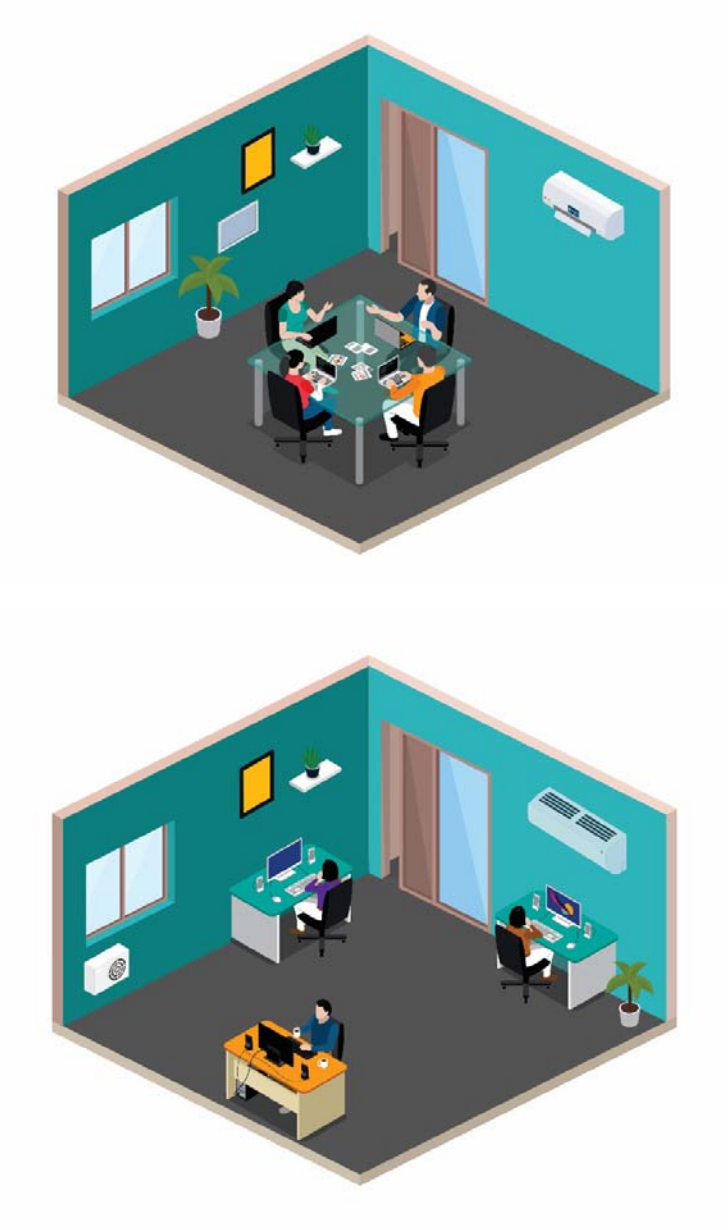
**AC – Air Conditioner, # HEPA- High Efficiency Particulate Air, $ UVC – Ultra Violet C rays, ǂ SARS-CoV – Severe Acute Respiratory Syndrome Corona Virus 2, ^ PPE – Personal Protective Equipment, **PVC – Polyvinyl Chloride, ## AHU Air Handling Unit, $$ CFM – Cubic Feet per Minute, ǂǂACH Air Exchanges per Hour*



Supplementary Fig. 1 Minimising risk of transmission- All wear masks, HCW with goggles-PPE, Exhaust ventilation-aerosols exhausted, droplets on various surfaces and AC directed from clean to contaminated.



Supplementary Fig. 2 Conversion of existing ICU to isolation room. Air duct containing dirty air should be blocked. Air Handling Unit [AHU] should provide fresh gas as much as possible. Install a negative pressure exhaust system.



Supplementary Fig. 3. In figure a there is no exhaust fan and occupants of chair face will be directed towards each other whereas in picture b is chair are arranged facing wall and exhaust fan has been installed

Challenges in Chronic Genetic Disorders: Lessons From the COVID-19 Pandemic

To examine the impact of the COVID-19 pandemic, we interviewed 26 patients with lysosomal storage disorders receiving enzyme replacement therapy. 20 (77 %) had significant interruption in their treatment, with an average of 8 (range 2-28) missed doses. Alternate methods of delivering uninterrupted care including home therapy were used. Vulnerable patients with chronic genetic disorders require organization for their multidisciplinary needs of care.

Keywords: *Enzyme replacement therapy, Lysosomal storage disorders.*

The unprecedented COVID-19 epidemic had healthcare at its epicenter. SARS-CoV-2 infection has been reported to have a worse outcome in patients with co-morbidities [1]. Patients with genetic disorders having multisystem involvement comprise a vulnerable high risk population [2]. Over the years, with improved awareness and advocacy, some patients with lysosomal storage disorders (LSD) receive intravenous infusions of enzyme replacement therapy (ERT) [3]. This management and associated multidisciplinary care are ordinarily challenging with significant impact on the family [4]. With the strict nationwide lockdown, we hypothesized that the pandemic brought new challenges for these patients. To evaluate the multifaceted impact on LSD patients receiving ERT, we carried out this telephonic survey using a dataset questionnaire.

Twenty six patients (20 males) receive ERT from our center. Their median (range) age was 18 (3-53) years. The average (range) duration of ERT was 5.6 years (2 months to 12 years). Eleven patients with Gaucher disease (42%) were receiving imiglucerase or velaglucerase, five each (19%) with MPS I and Fabry disease receiving laronidase and agalsidase beta, respectively, three (12%) with MPS II receiving idursulfase and two (8%) with Pompe disease receiving alglucosidase α.

Twenty patients (77%) had an interruption of two or more doses of ERT, while one patient missed a single dose. An average of 8 doses (range 2 to 28) were missed of a total of 28 doses for weekly infusion and 14 doses for two weekly infusion that should have been received during the study period. Two patients experienced a delay of one week in their regular schedule. One Fabry disease patient had to delay the start of his ERT. Two patients (7.7%) did not experience any interruption in their schedule and both were below 18 years of age under parental supervision. Of 20 patients who missed multiple doses, thirteen (65%) could not collect the medicine from the tertiary centre due to lack of transportation, while for two (10%) the medicine import was delayed. Four patients did not get the infusion as the local hospital had closed and one patient avoided going to the hospital for fear of infection **(Fig. 1)**. Two patients each of Fabry and Gaucher disease switched to home based ERT and two more patients specifically mentioned wanting to do the same.

Most patients did not report any acute worsening or new symptoms. One Fabry disease patient experienced increased pain and a rising serum creatinine level and one patient with Gaucher disease reported increased weakness and bone pain. Twelve patients or their parents (46%) reported anxiety and fear of the ongoing pandemic. Of these, 66% complained of constant worry, that exacerbated during hospital visits for ERT, while others combated their fear by strict adherence to social distancing and use of masks.

Majority of our patients missed multiple doses of ERT. The medicines are imported on a named patient basis and maintained at the tertiary care centre. These are collected at predefined intervals and infused at a local health care facility. The patients are followed up at 3-6 monthly intervals at the tertiary-facility. Most patients were unable to reach the tertiary facility due to lack of transportation and the centers being far away.

In contrast to Western countries, there is no system for home-based ERT in India. The pandemic created a need wherein patients and families identified local means to continue infusions. Studies from countries in Europe showed significant interruption in hospital-based ERT in up to 49% LSD patients in Italy and 25% of Gaucher disease patients in Spain, while patients on home therapy received regular treatment [5,6]. In our study, 15% patients switched to home-based therapy while an additional 7.7% wished to do so. The constant fear faced by patients' families for the affected member contracting COVID-19 infection was increased during hospital visits due to increased risk of exposure.

The long term impact of ERT interruption needs follow up. Previous experience with ERT interruption is limited and suggests that after restarting ERT, clinical deterioration may not be completely reversible [7-9]. While ERT is largely considered

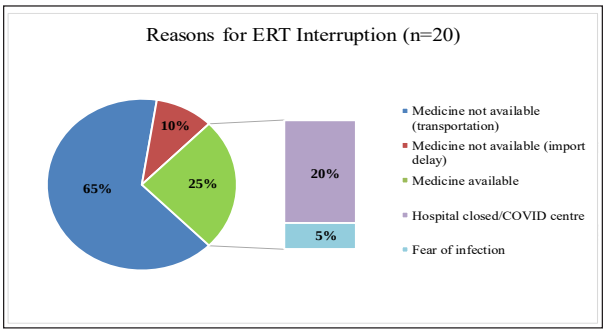


Fig. 1 Patients with significant interruption in enzyme replacement therapy and causes for the same.

safe, adverse events are reported. Though the circumstances promoted the shift to home based therapy, we wonder if the preparedness is adequate.

The bi-annual surveillance with clinical examination and blood and radiological investigations were missed by all twenty-six patients. As the therapy is relatively new, expensive, with stringent storage requirements, management is through tertiary care centres and primary care physicians are mostly not involved in patient treatment and follow-up. This lack of experience and awareness at the peripheral health centres impacted local management for these patients.

This study highlights pertinent aspects of interruption to care, anxiety and concerns of patients and their families with chronic genetic disorders, and the limitations of a tertiary care centric management for chronic disorders. The emerging role of telemedicine as an important tool for follow up and care of patients with chronic disorders is important. As we strive to increase access to ERT, we recognize the need to equip peripheral centres for care of patients with genetic disorders along with consultation with tertiary centres.

As the pandemic continues, we still grapple without guidelines to manage chronic genetic disorders. There is an urgent need to draw the attention of medical authorities to facilitate multi-specialty care for these patients to prepare for similar unforeseen situations.

Ethical clearance: No. IEC SGRH; EC/12/20/1784, dated January 12, 2021.
Contributors: SP, SB: conception of work, acquisition, analysis and interpretation of data, drafting and revising the work; SBM: drafting and revising the work; ICV: drafting the work and revising it critically for important intellectual content; RDP: conception and design of work, Interpretation of data, drafting and revising the work. All authors approved the final version of manuscript.
Funding: None for this study*; Competing interests*: None stated.

SWASTI PAL, SAMEER BHATIA, SUNITA BIJARNIA-MAHAY, ISHWAR C VERMA AND RATNA DUA PURI*
Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, India.
**ratnadpuri@yahoo.com*

REFERENCES

1. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.
2. Elmonem MA, Belanger-Quintana A, Bordugo A, et al. The impact of COVID-19 pandemic on the diagnosis and management of inborn errors of metabolism: A global perspective. Mol Genet Metab. 2020:S1096-7192(20)30195-5.
3. Muranjan M, Karande S. Enzyme replacement therapy in India: Lessons and insights. J Postgrad Med. 2018;64:195-99.
4. Hamad L, Kreidieh K, Nakouzi G, Lyon E, Yazbek S. Recommended measures for the efficient care of patients with genetic disorders during the COVID-19 pandemic in low and middle income countries. Am J Med Genet A. 2020 Oct 16. doi:10.1002/ajmg.a.61879 [Epub ahead of print].
5. Sechi A, Macor D, Valent S, et al. Impact of COVID-19 related healthcare crisis on treatments for patients with lysosomal storage disorders, the first Italian experience. Mol Genet Metab. 2020;130:170-71.
6. Andrade-Campos M, Escuder-Azuara B, de Frutos LL, Serrano-Gonzalo I, Giraldo P. Direct and indirect effects of the SARS-CoV-2 pandemic on Gaucher Disease patients in Spain: Time to reconsider home-based therapies? Blood Cells Mol Dis. 2020;85:102478.
7. Giraldo P, Irún P, Alfonso P, et al. Evaluation of Spanish Gaucher disease patients after a 6-month imiglucerase shortage. Blood Cells Mol Dis. 2011;46:115-8.
8. Solano M, Fainboim A, Politei J, et al. Enzyme replacement therapy interruption in patients with Mucopolysaccharidoses: Recommendations for distinct scenarios in Latin America. Mol Genet Metab Rep. 2020;23:100572.
9. Politei J. Fabry disease during the COVID-19 pandemic. Why and how treatment should be continued. Mol Genet Metab. 2020;130:227-29.

Appropriateness of Lower Waist Circumference Cutoffs for Predicting Derangement in Metabolic Parameters Among Asian Children and Adolescents: A Pilot Study

Waist circumference (WC) >90th percentile cut-off effectively screens children for metabolic syndrome, as some specific metabolic derangements (high fasting serum levels of insulin and triglycerides) may be better associated with lower (70th percentile) waist circumference cut off. We evaluated a subset of children and adolescents found obese or overweight following the anthropometric screening in a school-based survey. Metabolic parameters (fasting insulin levels, fasting blood sugar and fasting lipid profile and blood pressure) were compared among 3 groups of obese or overweight children divided on the basis of WC percentiles (>90th, 70th-90th and <70th). 78 children (aged 11-18 years, 45 boys) were evaluated. The proportion of participants with high triglycerides and fasting insulin among those with WC<70th (28.6%, 19%) was significantly lower than that in the group with WC >90th (76.9%, 53.8%) as well as in group with WC 70th-90th percentile (38.7%, 41.9%).

Keywords: *Anthropometry, Blood sugar, Central obesity, Overweight, Triglycerides.*

Obese children from south Asian region are relatively more prone to develop components of metabolic syndrome [1]. Waist circumference is a widely accepted and practical tool for community screening of obesity [2]. However, certain concerns have been raised over the cutoff being used while utilizing waist circumference as a predictor of metabolic syndrome [3,4]. We explored the suitability of lower waist circumference cutoff

(70th percentile, WC70) relative to standard (90th percentile, WC90) for screening components of metabolic syndrome among children and adolescents.

The study was performed at a tertiary care teaching institute in Northern India between October, 2015 and March, 2017 as a part of a school-based survey. Students aged between 9 and 18 completed years from four schools catering to middle and upper middle class population (2 private and 2 government managed) were screened for anthropometric parameters. Those found to be obese or overweight were enrolled if parents provided informed consent. Study was performed following approval from Institute ethics committee as well from school administration.

Children were screened for height (portable stadiometer, IndoSurgicals) and weight (Omron HN-286 digital weight scale). Waist circumference was measured at midpoint between the lowest rib and the iliac crest in a horizontal plane after complete expiration by using non-elastic tape to the accuracy of 0.1 cm. Fasting blood samples were collected at school and assessed using colorimetric method (Beckman Coulter AU 680) for blood sugar and lipid profile. Fasting insulin was measured as an additional metabolic marker [5]. Blood pressure was measured thrice using mercury sphygmomanometer and regional reference data was used to define hypertension [6]. The components of metabolic syndrome were recorded as WC90 along with presence of 2 or more of the following: Hypertriglyceridemia >150 mg/dL, high density lipoprotein (HDL) cholesterol <40 mg/dL, high blood pressure >90th percentile and fasting blood glucose >100 mg/dL [7].

The sample size was as per availability, since the number of participants with parental consent for invasive procedure was expected to be limited. Statistical analysis was performed using IBM SPSS version 20. The data from the participants who were screened for metabolic syndrome was divided into three groups based upon waist circumference (>WC 90th, 70th-90th percentile and <WC70) as per IAP reference data [8]. The proportion of children with derangement in various metabolic parameters were compared among the groups.

Among 1958 children screened for anthropometric parameters, 24.6% boys (8.5% obese) and 22.9% girls (7.8% obese) were either obese or overweight as per BMI criteria. Parents of only 78 (aged 11-18 years, 45 boys) of 469 obese/ overweight children provided consent for blood sampling. When these 78 participants were divided on the basis of waist circumference percentiles, 26 had >WC90 (group I), 31 had waist circumference between 70th-90th percentile (group II) and 21 had <WC70 (group III). The number of participants with obesity were 19, 17 and 16, respectively among the group I, II and III.

The WC >90th percentile significantly differentiated children with high diastolic BP as well as those with two or more deranged parameters from others (**Table I**). However, both group I and II had similar proportion of participants with high triglycerides (TG) and high fasting insulin, which was significantly higher compared with group III.

Table I Proportion of Participants With Deranged Metabolic Parameters Among Groups Divided on the Basis of Waist Circumference Percentiles

Parameter	*Group I (n=26)*	*Group II (n=31)*	*Group III (n=21)*
High systolic BP	13 (50)	9 (29)	8 (38.1)
High diastolic BP[a]	6 (23.1)	2 (6.5)	2 (9.5)
High fasting blood glucose	9 (34.6)	6 (19.4)	5 (23.8)
High triglycerides[b]	20 (76.9)	12 (38.7)	6 (28.6)
Low HDL	20 (76.9)	21 (67.7)	15 (71.4)
High LDL	13 (50)	13 (41.9)	5 (23.8)
≥2 components of MS[c]	23 (88.5)	16 (51.6)	11 (52.4)
High fasting insulin[d]	14 (53.8)	13 (41.9)	4 (19)

Value in number (%). BP: blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein; aP: for group I vs group II; P=0.045; bP= for group I+II vs group III, P= 0.017; cP=for group I vs group II; P=0.001; dP=for group I+II vs group III, P=0.012; Participants divided based on waist-circumference >90th centile (Group I); 70th - 90th centile (Group II) and <70th centile (Group III).

The presented data indicate that though WC >90th percentile cutoff effectively screen children for metabolic syndrome, some specific metabolic derangements (high fasting serum levels of triglyceride and insulin) may be better associated with lower (70th percentile) waist circumference cutoff.

In a recent systematic review, it has been concluded that waist circumference has better accuracy than BMI in predicting clustered cardiometabolic risk factors [9]. However, some studies points towards few gaps in the knowledge about its utility as a screening tool. Horlick and Hediger emphasized on the need to explore various waist circumference cutoff points while evaluating metabolic syndrome in different population groups [3]. A recent cross sectional analysis involving more than 6000 adolescents explored the appropriateness of using different waist circumference percentile cut of points for predicting various metabolic syndrome parameters. The optimal waist circumference percentile to identify youth with elevated insulin was 92nd and that to identify youth with ≥3 risk factors was 85th [4]. Using the unconventional WC cut off, we noticed the proportion of participants with high triglycerides and fasting insulin among those with WC<70th (28.6% and 19%) was significantly lower than that in the group with WC >90th (76.9% and 53.8%) as well as in group with WC 70th-90th percentile (38.7% and 41.9%). Though derived from small number of participants, this novel interesting finding deserves further systematic exploration with better designed studies. Our findings suggest that 70th percentile of waist circumference may be more sensitive in predicting derangements in serum insulin and triglyceride level than 90th percentile.

Ethics clearance: Institute ethics committee of AIIMS, Rishikesh; No 29/IM/2013 dated September 07, 2013.
Contributors: BKB, JPG: Study concept and design; RG: acquisition of data; NL,VK: analysis and interpretation of data;

JPG: obtained funding; RG, JPG: drafting of manuscript; BKB, NL: Statistical analysis; BKB,VK: Final reviewing and editing. *Funding:* Intramural funding of AIIMS, Rishikesh. *Competing interests:* None stated.

RAJEEV GOYAL,[1] BHANU KIRAN BHAKHRI,[2*] JAGDISH PRASAD GOYAL,[2] NIKHIL LOHIYA[3] AND VAMAN KHADILKAR[3]
Department of [1]Biochemistry and [2]Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand; and [3]Pediatric Endocrinologist, HCJMRI, Jehangir Hospital, Pune, Maharashtra; India
[*]drbhanu04@gmail.com

REFERENCES

1. Brown T, Smith S, Bhopal R, Kasim A, Summerbell C. Diet and physical activity interventions to prevent or treat obesity in South Asian children and adults: A systematic review and meta-analysis. Int J Environ Res Public Health 2015;12:566-94.
2. Perona JS, Schmidt-RioValle J, Rueda-Medina B, Correa-Rodríguez M, González-Jiménez E. Waist circumference shows the highest predictive value for metabolic syndrome, and waist-to-hip ratio for its components in Spanish adolescents. Nutr Res. 2017;45:38-45.
3. Horlick M, Hediger ML. Measurement matters. J Pediatr. 2010;156:178-9.
4. Bauer KW, Marcus MD, El Ghormli L, Ogden CL, Foster GD. Cardio-metabolic risk screening among adolescents: Understanding the utility of body mass index, waist circumference and waist to height ratio. Pediatr Obes. 2015;10:329-37.
5. Garg MK, Tandon N, Marwaha RK, Singh Y. Evaluation of surrogate markers for insulin resistance for defining metabolic syndrome in urban Indian adolescents. Indian Pediatr. 2014;51:279-84.
6. Raj M, Sundaram R, Paul M, Kumar K. Blood pressure distribution in Indian children. Indian Pediatr. 2010;47:477-85.
7. Zimmet P, Alberti KG, Kaufman F, et al. IDF Consensus Group. The Metabolic Syndrome in Children and Adolescents - an IDF Consensus Report. Pediatr Diabetes. 2007;8:299-306.
8. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, Agrawal KK, et al. Revised IAP Growth Charts for Height, Weight and Body Mass Index for 5 to 18-Year-Old Indian Children. Indian Pediatr. 2015;52:47-55.
9. Lichtenauer M, Wheatley SD, Martyn-St James M, et al. Efficacy of anthropometric measures for identifying cardiovascular disease risk in adolescents: Review and meta-analysis. Minerva Pediatr. 2018;70:371-82.

Utility of Body Mass Index Quick Screening Tool for Assessing Nutritional Category of Children

Body mass index (BMI) quick screening tool was used on retrospective data of 415 boys and 428 girls (8-14 years). Sensitivity and specificity of the BMI tool were assessed by comparing with the Indian Academy of Pediatrics BMI charts. The BMI tool had high sensitivity and specificity to identify children with normal BMI and underweight. However, its sensitivity varied between 50-57.4% for overweight and obese children, respectively.

Keywords: *Growth chart, Underweight*

The double burden of malnutrition, defined as the simultaneous manifestation of both undernutrition and overweight and obesity, has increased in most low-income and middle-income countries [1]. It is important to identify both undernutrition and overnutrition so that preventive and corrective measures can be implemented at the earliest.

The Indian Academy of Paediatrics (IAP) Revised Growth Charts 2015 are recommended for assessment of growth in children between 5-18 year of age and provide body mass index (BMI) charts to screen for under or over-nutrition [2]. In a busy paediatric practice, it has been observed that weight and height are recorded but BMI is overlooked as it is not calculated [3]. This poses a risk of missing undernutrition, overweight and obesity which if undiagnosed have serious consequences on the health of the child.

Recently gender-specific BMI quick screening tool (children ≥8years) [4] has been developed which overcomes this problem of computing the BMI. The child can be identified as underweight, normal weight, overweight and obese by plotting the weight and the height. The present study was planned to assess the utility of this BMI quick screening tool in terms of sensitivity and specificity by comparing with the Revised IAP BMI charts.

The BMI tool [4] was used as per the recommendation on the retrospective data of children and adolescents in the age group 8-14 years (unpublished data). The height and weight were plotted on X-axis and Y-axis, respectively. The meeting point of the two lines gave the BMI. Depending on where the BMI point rested, the child was classified as being obese, overweight, normal BMI or underweight. BMI was also calculated and plotted on the IAP BMI charts [2], and nutritional status identified.

Statistical analyses were conducted using SPSS version 26 (SPSS Inc). Frequency (percentage) of underweight, normal BMI, overweight and obesity were calculated using BMI quick-screening tool and Revised IAP BMI chart. Sensitivity and specificity of the BMI quick-screening tool against IAP charts were calculated.

Data on 843 (415 boys) children and adolescents were analyzed. The mean (SD) age of boys and girls was 10.8 (1.7) and 10.8 (1.6) years, respectively. According to BMI quick-screening tool, 9.88% of boys were underweight, 72.87% had normal BMI, 12.05% were overweight and 5.3% were obese. As per IAP BMI charts, the percentage of boys with underweight, normal BMI, overweight and obesity was 4.34%, 68.67%, 18.55%, 8.43%, respectively. According to BMI

Table I Gender-wise Sensitivity and Specificity of BMI Quick Screening Tool Compared to Revised IAP BMI Charts

BMI category	*Boys*		*Girls*	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
Underweight	83.33% (58.58-96.42)	97.98% (96.06-99.12)	100.00% (79.41-100.00)	97.09% (94.97-98.49)
Normal BMI	97.18% (94.53-98.78)	70.0% (61.34-77.72)	95.59% (92.58-97.63)	72.93% (64.55-80.27)
Overweight	53.25% (41.52-64.71)	94.96% (92.05-97.03)	57.47% (46.41-68.01)	95.31% (92.49-97.29)
Obese	51.43% (33.99-68.62)	100.0% (99.03-100.00)	50.0% (31.30-68.70)	99.75% (98.61-99.99)

BMI-body mass index.

quick-screening tool, 11.92% of girls were underweight, 71.26% had normal BMI, 13.79% were overweight and 3.04 % were obese. According to the IAP BMI charts, the percentage of girls with underweight, normal BMI, overweight and obesity was 4.67%, 67.77%, 20.56% and 7.01%, respectively. The sensitivity and specificity of the BMI quick screening tool is shown in **Table I**.

The BMI tool had high sensitivity and specificity to identify children with normal BMI and underweight. However, its sensitivity varied between 50-57.4% for overweight and obese children. It was observed that a proportion of children and adolescents with normal BMI by the BMI quick tool were overweight as per IAP BMI charts. Similarly, a proportion of the children diagnosed as overweight by the tool were in the obese category as per the BMI charts. This significant false-negative group needs to be identified accurately as they may progress towards the health risks associated with overweight and obesity. Utility of this tool can be evaluated in comparison with other obesity indices like waist circumference and weight/height ratio.

Use of BMI quick screening tool alone for the identification of overweight and obesity will leave a significant proportion of undiagnosed children. Whether the sensitivity be improved with help of a statistical tool, such as revising the cutoff percentiles to match the accuracy of BMI charts needs to be explored. BMI cutoff with higher sensitivity and minimal false-negative proportion will be of great benefit.

Acknowledgement: Dr. Vaman Khadilkar, Jehangir Hospital, Pune and Bombay Hospital, Mumbai for providing the BMI quick screening tool.

Ethics clearance: Bhabha Atomic Research Centre Hospital Medical Ethics Committee; No. EC/NEW/INST/2020/790 dated 27 May, 2020.

Funding: None; *Competing interest*: None stated.

SANGEETA P SAWANT

Department of Pediatrics,
Bhabha Atomic Research Centre Hospital,
Anushakti Nagar, Mumbai, Maharashtra 400 094, India.
drsawantsangeeta@gmail.com

REFERENCES

1. Popkin BM, Corvalan C, Grummer-Strawn LM. Dynamics of the double burden of malnutrition and the changing nutrition reality. Lancet. 2020;395:65-74. DOI:https://doi.org/10.1016/S0140-6736(19)32497-3.
2. Indian Academy of Pediatrics Growth Charts Committee. Khadilkar V, Yadav S, Agrawal KK, et al. Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Indian Pediatr. 2015;52:47-55.
3. Smith S, Reji E. Doctor's attitudes to and knowledge and usage of growth charts. S Afr Fam Pract. 2015;57:219-22.
4. Khadilkar V, Lohiya N, Chiplonkar S, Khadilkar A. Body mass index quick screening tool for Indian Academy of Pediatrics 2015 growth charts. Indian Pediatr. 2020;57:904-06.

Increased Screen Time – A Pandemic Era Trigger for Neuro-Cardiogenic Syncope

The COVID-19 pandemic has resulted in a revamp of our everyday life, which is being dubbed as the new normal. As people get adjusted to work and study from home, there are new challenges in maintaining physical and mental health. An unusual pattern noted by the author is an increase in the number of children diagnosed with autonomic syncope in recent months. Between August and November, 2020, 16 children were diagnosed with neuro-cardiogenic syncope in the author's clinic, as compared to only three children during the same period in 2019. The age group of these children varied between 7-16 years. All children were subject to a detailed history regarding the event as well as potential red flag signs [1]. All episodes happened during the daytime and when the children were either seated or standing. None of the episodes happened during an exertion; although, in one child, there were three episodes that happened immediately after an exertion. Almost all episodes were preceded by a prodromal symptom which included light headedness, aura and/or vertigo. There was a prompt and complete recovery and there were no injuries. The children presented for evaluation after a median (range) time of 2 days (4 hours – 7 days) after the event. They underwent recording of postural vital signs and a standardized 12 lead electrocardiogram.

When enquired, each of the parents revealed a concern about increased daily screen time on smart devices for their children. The older children spent more time on the screen due to a cramped schedule of online classes while in the younger children, smartphone use replaced other forms of physical activity curtailed by COVID-induced lockdowns. The family were counselled about lifestyle modifications including sleep hygiene, adequate water and salt intake and reduction of screen time. Further evaluation for autonomic syncope was not carried out. All parents were contacted three to six months after their presentation to assess the efficacy of the intervention. The parents reported compliance with the suggested lifestyle measures and no recurrence of syncope during the short period of follow-up.

Neuro-cardiogenic syncope is common in children with 1 in 6 children reported to have at least one episode before adulthood [2]. It is possible that the increased screen time and exposure to high-definition screens results in increased eye strain and fatigue which reduces the threshold for fainting. In particular, high color temperature display and display flickering have been shown to cause eye fatigue [3]. Dizziness and pre-syncope have previously been reported to be potential adverse events of smartphone use, and syncope is likely an extension of the same pathophysiological process [4].

The findings are based on personal observations in clinical practice and highlight the importance of a detailed history in evaluation of syncope. Prospective studies with assessment of multiple associated factors of syncope may elucidate this issue further. However, till that time, pediatricians should continue to counsel the parents about the importance of limiting screen time in children.

MANI RAM KRISHNA
Dr RK Hospital for Women and Children,
Thanjavur, Tamil Nadu, India.
mann_comp@hotmail.com

REFERENCES

1. Krishna MR, Kunde MF. A clinical approach to syncope. Indian J Pract Pediatr. 2020;22:92-9.
2. McHarg ML, Shinnar S, Rascoff H, Walsh CA. Syncope in childhood. Pediatr Cardiol. 1997;18:367-71.
3. Seltman W. Prevent eyestrain from digital devices [Internet] WebMD LLC; c2005-2021. [updated 2019 August 6]. Available from *https://www.webmd.com/eye-health/prevent-digital-eyestrain*.
4. Al-Khlaiwi T, Meo SA. Association of mobile phone radiation with fatigue, headache, dizziness, tension and sleep disturbance in Saudi population. Saudi Med J. 2004;25:732-6.

Should High Flow Nasal Cannula Therapy Be the Primary Mode of Respiratory Support in a Pediatric Intensive Care Unit? Questions Remain!

We read with interest the recent paper on high flow nasal cannula (HFNC) therapy as a primary mode of respiratory support in a pediatric intensive care unit (PICU) [1]. To better understand the paper, we request response to the following queries:

i) As the aim of the study was to assess the efficacy of HFNC as the primary mode of respiratory support in PICU, we think that a cross sectional study design was inappropriate. Instead, a randomized controlled trial (RCT) study design, if used, would have given clearer answers. In the RCT, other modes of non-invasive ventilation (NIV) could have been used as the comparator and the primary outcome measured could have been the percentage of children going on to invasive mechanical ventilation.

ii) The authors mention targeting oxygen concentration between 92-97% for all children between 1 month to 16 years? Is there a validated reference or protocol for adjusting FiO_2 to target such a saturation up to 97%?

iii) The exclusion criteria do not mention children with congenital cyanotic heart disease. Should this group not have been excluded as the methodology adopted required monitoring of oxygen saturation and adjustment of FiO_2 to keep arterial oxygen concentration between 92-97% and for calculation of saturation to FiO_2 (SF) ratio.

iv) We also want to know more about the Respiratory Clinical Score that was used to monitor the study children. This scoring system, as per our understanding, was not meant for use in children admitted to the PICU and on respiratory support [2]. Similarly, we also want to know about validation of this tool in Indian children? We feel that assessment of dyspnea using respiratory clinical score in children on HFNC would have been incorrect as the given score has many points like – "hyperactivity, increased coughing after play, decreased appetite" which cannot be assessed in the PICU and some scores like "agitation" are likely to be scored higher in the PICU setting with a child on respiratory support.

v) On going through the original article [3], with regard to use of COMFORT score, which in this study was used for assessing the tolerability of HFNC, we find scores for respiratory support which use responses that include "respiratory response" which is scored using terms like "resistance to ventilator, actively breathes against ventilator, fights ventilator etc" similarly other heads like "muscle tone assessment facial tension assessment" which are inappropriate in this setting/would have yielded inappropriate results. Modifications of this scoring system to use it to determine sedation and dose adjustments that need to be done depending on the assessed score. There is no mention about use of this score to change the dose of sedation or if the original score was used it may not again be appropriate.

vi) We would also want to know how the authors derived the determined sample size and assumed 50% risk reduction and achieved the same in exactly one year.

vii) **Table I** mentions the total number of children in HFNC responders' group to be 188 [1]. But on totalling the number of cases across diagnoses, the total sums up to only 186. There thus is missing data of 2 children. There are 2 extra diagnoses amongst the non-responders having 19 diagnoses versus 17 children. Even though we did consider the same child to have more than one diagnosis in the non-responder group, but having two less diagnoses compared to the total number of children in the responder group left us perplexed.

IK KARTHIKA AND JOSEPH JOHN*
Department of Pediatrics, AIIMS, Bhubaneswar, Odisha.
**ped_joseph@aiimsbhubaneswar.edu.in*

REFERENCES

1. Shah S, Kaul A, Bhosale R, Shiwarkar G. High flow nasal cannula therapy as a primary mode of respiratory support in a pediatric intensive care unit. Indian Pediatr. 2021;58:41-43.
2. Liu LL, Gallaher MM, Davis RL, et al. Use of a respiratory clinical score among different providers. Pediatr Pulmonol. 2004;37:243-8.
3. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: The COMFORT scale. J Pediatr Psychol. 1992;17:95-109.

AUTHOR'S REPLY

We thank the readers for their interest.

i) We agree that an RCT would have been ideal clinical design. If a comparator group of NIV is used, then there is a possibility of unnecessarily exposing large number of children to this modality when they could be successfully managed on lesser invasive support.

ii) The PALICC guidelines mention targeting a saturation of 92-97% in children with mild ARDS [1]; similar targets have also been used in other studies [2]. For calculation of SF ratio, the PALICC guidelines recommend titrating FIO2 to keep SpO2 between 92-97%.

iii) Children with cyanotic heart disease were excluded.

iv) A respiratory clinical score with the following parameters was calculated: age specific respiratory rate scores 0 to 3, retractions 0 to 3, dyspnea 0 to 3, and wheeze 0 to 3. Total score ranged between 0 for normal and 12 at the extremes. This score has been used in the PICU to assess effectiveness of HFNC [3]. The score has not been validated in Indian children but there is no plausible reason to believe that RR, retractions, wheezing or dyspnea would be different in Indian children.

v) COMFORT score has also been used in non-ventilated patients in the PICU [4].

vi) For calculation of sample size, a baseline risk for need of ventilation as 16% was assumed in children with respiratory distress presenting to the emergency [5]. We hypothesised that HFNC would reduce the risk by 50% (absolute reduction of 8 percentage points). Using alphaerror of 0.05 and for 90% power, we calculated a sample size of 178. To allow for potential 10% recruitment failure rate, required sample size was increased to 200.

vii) We agree that numbers add to 186 for diagnosis, and regret the typographical error.

AMITA KAUL
amitakaul@hotmail.com

REFERENCES

1. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16:428-39.
2. Milesi C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure for the initial respiratory management of acute viral bronchiolitis in young infants: A multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med. 2017:43: 209-16.
3. Spentzas T, Minarik M, Patters A, Vinson B, Stidham G. Children with respiratory distress treated with high flow nasal cannula. J Intensive Care Med. 2009;24:323-8.
4. Dijka MV, Boera JB, Kootb HM, et al. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain. 2000;84:367-77.
5. Wing R, James C, Maranda LS, et al. Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in pediatric acute respiratory insufficiency. Pediatr Emer Care. 2012;28:1117Y112.

NEWS IN BRIEF

A beacon of hope for patients with epilepsy

Epilepsy is a neurological disorder frequently seen in the clinical setting. A patient with epilepsy lives with fear and anxiety about the uncertainty of the seizure episodes that might prove fatal when it strikes during certain activities likedriving or swimming.

A research team from California has come up with a new seizure predicting mathematical model that can precisely warn epilepsy patients five minutes to one hour before they are likely to experience a seizure. The researchers used implantable devices that offered ongoing real-time intracranial electro encephalogram (EEG) monitoring. The mathematical model can use this data and assess unique brain signals from each patient, looking out for patterns of activity that show a pre-ictal state, in which the patient is at risk of seizures.

A timely warning of seizures provides an opportunity for epileptics to safeguard themselves – they can avoid driving or moving about or can take a dose of antiepileptics. This also paves way for other interventions like responsive electrical stimulation in which seizure signals are detected and electrical stimulation is sentto the brain through an implantable device to prevent the seizure from happening.This research could prove to be a game changer for these patients.
(Journal of Neural Engineering, 26 February 2021)

Does blood group influence COVID-19 infection?

Not all individuals seem to be equally susceptible to infection with SARS-CoV-2. Multiple factors might be responsible for this differential susceptibility, ABO blood group being one among them. A possible link between ABO blood groups with COVID-19 susceptibility and severity has been shown in multiple studies with contrasting results.

Researchers focussed on the receptor binding domain (RBD) of SARS-CoV-2 and assessed how it interacted with respiratory and red blood cells (RBCs) in A, B and O blood types. They found that theRBD bound preferentially to blood group A found on respiratory cells, but had no predilection for blood group A RBCs, or other blood groups found on respiratory or RBCs.

Thisfinding may provide insight into the possible link between blood group A and infection with COVID-19. Further understanding of mechanisms of interaction of the virus with blood groups might enable discovery of newer therapies or methods of prevention.
(Blood Advances, 3 March 2021)

Precarious behavior post COVID-19 vaccination: The Peltzman effect

The COVID-19 pandemic has familiarized people with the concept of 'risk compensation' – behavioral modification to curtaildamage in risky circumstances. People washed hands frequently, wore masksand socially distanced themselvesas cases skyrocketed. However, this practice has whittled away as the novelty of the threat faded, resulting in 'pandemic fatigue' manifesting as reduced adherence to safety measures. As COVID vaccines are rolled out, there has been increasing optimism and euphoria among people anticipating the end of the pandemic. This has further intensified risky behavior and challenged public health efforts.

In 1975, Sam Peltzman, an economist from the University of Chicago, described the 'Peltzman effect' – people show a compensatory increase in risky behavior with introduction of safety measures. Better road safety regulations would tempt people to indulge in risk-taking behavior once they feel that situations are safer.This effect identifies four major contributors to risk compensation, all of which are present in the COVID-19 pandemic: *i*) The new safety measure should be visible (people being vaccinated are aware of the fact); *ii*) People must be motivated to engage in risky behavior (many yearn to return to pre-pandemic lifestyle after a year of lockdown); *iii*) People must have the control to increase risky behavior (people are free to move post relaxation of lockdown); and *iv*) The safety measure has to be effective (with presumably efficacious vaccines, many have a sense of security). As the number of vaccinated people rises, people would have a misleading sense of security in "herd immunity" long before it is actually present.

As we step into a new stage of the pandemic, marked by both the ongoing vaccination and the emergence of novel virus variants, an amelioration of safety measures might sadly concur with upsurge of viral spread. Hence, steps need to be taken to tackle possible harms from the Peltzman effect. Enforcing risk-avoiding behavior post vaccination is less likely to be effective. Risk reduction, rather than total abstinence, seems a more feasible alternative. Prioritizing mask-wearing, irrespective of vaccination status, might have the greatest public health benefit. This might need a compromise on other restrictions, like allowing gatherings with vaccinated individuals. Lack of timely measures might allow the virus to ravage the globe.
(Annals of Internal Medicine, 2 March 2021)

JERIN C SEKHAR
drjerincsekhar@gmail.com

IMAGE

Childhood Linear Focal Elastosis

A 12-year-old boy presented with asymptomatic linear skin lesions over the back. There was no history of exercise, trauma, excessive or rapid weight gain or loss, and topical or systemic drug use. Examination showed multiple transverse, slightly elevated, yellow streaks of varying lengths over back (**Fig. 1**). A diagnosis of linear focal elastosis (LFE) was made. Parents were counselled and no specific therapy was initiated.

LFE is a benign condition characterised by asymptomatic yellowish, palpable linear striae over middle and lower back. LFE classically occurs in older males and has rarely been reported in children less than 15 years. Exact pathogenesis is not known, though both degeneration and regeneration of elastic fibres is thought to contribute towards skin lesions. Differential diagnosis includes striae distensae which are white to pink coloured depressed skin lesions over abdomen, thigh and arms. Systemic associations have not been reported, and no treatment is usually required.

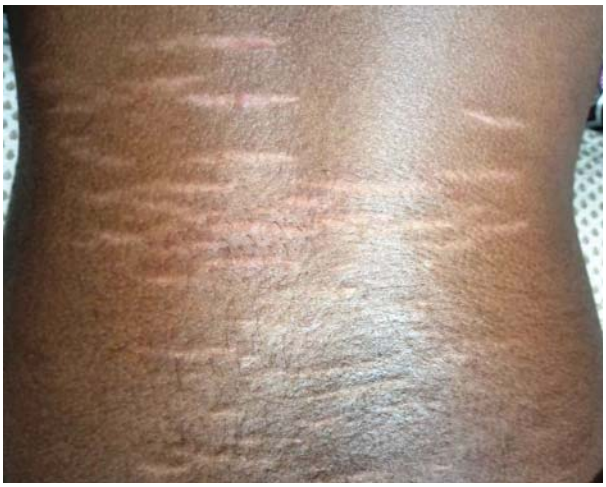
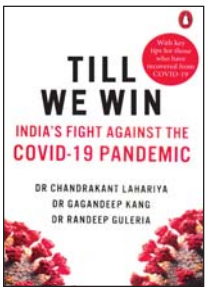


Fig. 1 Childhood linear focal elastosis.

Megha Garg[1] and Aman Gupta[2*]
Departments of [1]Dermatology and Cosmetology, and [2]Pediatrics, MEDENS Hospital, Panchkula, Haryana, India.
**drgupta_aman@yahoo.com*

BOOK REVIEW



Till We Win
India's Fight Against The Covid-19 Pandemic
Chandrakant Lahariya, Gagandeep Kang and Randeep Guleria
M/s. Penguin Random House, Gurgaon, Haryana, India.
Pages: 308; *Price*: Rs. 299/-.

A unique combination of authors (vaccine researcher, pulmonologist-cum-medical administrator and public health expert) has resulted in the publication of a well-edited paperback on COVID-19. The contents are appealing and addressed to not only the medical fraternity but also to the lay public.

Scientific facts on the epidemiology of the disease, lockdown, treatment options, vaccines and more importantly true versions of frontline workers' experience make the book very interesting and compelling to read. Detailed accounts of coordinated response by the government in tackling the pandemic in India have been elaborated comprehensively. The lessons learnt from the pandemic by the government, public health experts, healthcare workers and the common man have been described extremely well.

Practical tips on guidelines to follow after recovery and adjustments to the new normal state are very useful for the readers. The suggestions for strengthening our public health system are thought-provoking, and need serious consideration by the governmental agencies for early implementation.

From the pediatrician's point of view, one might feel that the impact of the pandemic on child health has not been adequately dealt with, more so because there is no discussion on MIS-C/PIMS-TS; although, this should not discourage them from going through this very well-written book.

S Balasubramanian
Department of Pediatrics, Kanchi Kamakoti Childs Trust Hospital,
Chennai, Tamil Nadu, India.
sbsped@gmail.com

Printed and published by Dr Devendra Mishra on behalf of Indian Academy of Pediatrics and printed at Cambridge Press, Kashmere Gate, Delhi-110006 and published at 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049. Editor: Dr Devendra Mishra

This is Kabir. For proper mental development & immunity he needs the strength of iron from the beginning

In IDA - Brain Development & Immunity

Livogen® BABY

Each ml contains Ferrous Ascorbate
eq. to elemental iron 10 mg, Folic acid IP 100 mcg

STRENGTH OF BLOOD COUNTS

Supports Brain development & Immunity[1,2]

- Offers **essential Iron & Folic acid** combination

Comprehensive formulation

- Offers **better response** rate
- Good **GI tolerability profile**

Fights symptoms of Iron deficiency[3]

- Offers right dose of Iron that helps in **RBC production** & **prevents IDA**[#,2,4]

1. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J. 2010;9:4. Published 2010 Jan 25. doi:10.1186/1475-2891-9-4
2. Pettifor JM, Ziotkin S (eds): Micronutrient Deficiencies during the Weaning Period and the First Years of Life. Nestlé Nutrition Workshop Series Pediatric Program, vol 54, pp 137–152, Nestec Ltd., Vevey/S. Karger AG, Basel, © 2004.
3. Cherayil BJ. Iron and immunity: immunological consequences of iron deficiency and overload. Arch Immunol Ther Exp (Warsz). 2010;58(6):407–415. doi:10.1007/s00005-010-0095-9
4. The Federation of Obstetric & Gynaecological Societies of India, FOGSI publication FOGSI FOCUS 2008- IRON DEFICIENCY ANAEMIA

Iron Deficiency Anaemia