SPECIAL ISSUE

Pediatrics

Asthma's Perfect Storm: Bacteria, Vitamin D, Stress, and Inflammation

Probiotics for Infant Colic & Kids' IBS

Green Spaces Improve Quality of Life and BMI

Iron Supplementation in Pregnancy and Infancy

IBS and Probiotic Treatment in Pediatric Patients

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MESSAGE FROM THE PUBLISHER

The Lifelong Impact of Integrative Pediatrics

Every medical specialty has its share of challenges and rewards. Pediatrics is no different. The pediatrician is often the very first doctor we are exposed to and that first encounter can stick with us for years after. A skilled pediatrician has the ability to relate to children and adolescents but also must address the information needs of the parents as well.

Pediatricians and family practitioners navigate a complex journey with their young patients, which includes constant movement through key growth stages. It’s an area of medicine in which integrative and naturopathic physicians can thrive.

While it is always a bit challenging to pick what gets to run in our special issues, our guest editor Matthew Baral, ND, did an outstanding job guiding this process. In addition, he also contributed this issue’s peer-reviewed paper on the complex topic of asthma and what integrative practitioners can do to help prevent and treat it.

This special issue is relevant not just to pediatricians, but to anyone who sees children in their practice. Our Abstracts & Commentary cover clinically relevant and diverse topics such as nature, prenatal sleep, iron supplementation, homeopathy, and probiotics. Our sponsored podcast is also on the topic of probiotics.

We hope you enjoy this special issue on pediatrics. Please share it with your colleagues and let us know what you think. Feel free to email me directly at Karolyn@IMPACThealthmedia.com. Thank you for your support of the Natural Medicine Journal!

Karolyn A. Gazella
Publisher, Natural Medicine Journal
Asthma’s Perfect Storm
Bacteria, vitamin D, stress, and inflammation

ABSTRACT
Asthma affects approximately 24 million Americans, and 6.3 million of those are under 18 years of age. The reliance on asthma medication as the only treatment for this widespread condition has had virtually no effect on asthma rates, which have continually increased since the 1980s. It is therefore imperative that the medical community at large start to commit to prevention as an equally important measure when considering asthma as a condition. A holistic perspective should take into account all the factors affecting asthma prevalence and expose the connections between them.

INTRODUCTION
Asthma is one of the most common chronic diseases in childhood, second only to dental caries. Like many chronic conditions seen in both children and adults, asthma may be preventable and treatable with lifestyle changes and environmental improvements. Historically, the predominant medical approach to asthma management has been through the use of medications such as corticosteroids, beta-agonists, leukotriene modifiers, anticholinergics, mast-cell stabilizers, methylxanthines, and anti-IgE monoclonal antibodies. These medications are unquestionably effective at curbing or eliminating the symptoms of asthma and saving lives. So effective, in fact, that little else has the same immediate treatment response. That consequently lessens the perceived need of preventive and nutritional maintenance measures. However, asthma medications are not without adverse effects. Associations between decreased bone mineral density and exposure to inhaled corticosteroids (ICS) have been reported. Most recently, ICS use for more than 6 months before 6 years of age proved to be a significant risk factor for decreased bone mineral density. Monoclonal antibody treatments, used in patients with severe and/or steroid-resistant asthma, have concerning adverse effects as well, including increased risk of cardiovascular and cerebrovascular events. Regardless, the FDA has approved 2 new monoclonal antibody treatments in the past year, one of which lists anaphylaxis and cancer as potential adverse effects. The leukotriene inhibitor montelukast has also been linked to neuropsychiatric events, including suicide and depression, although there may be contributing factors to this risk, which will be discussed later in this paper.

Ignoring the research on potential roots of inflammation and aggravation of symptoms in asthmatic patients may be detrimental to the efforts of the National Heart, Lung, and Blood Institute’s National Asthma Education and Prevention Program (NAEP). Remarkably, since its creation in 1991 there has not been a decline in emergency room visits, hospitalizations, or deaths in children with asthma. Despite the fact that asthma deaths overall have decreased, a trending increase in deaths due to asthma in children aged 0 to 4 years was seen from 1999 to 2009, implying that additional measures must be considered in the standards of asthma care. Additionally, asthma prevalence in children also trended upward in this same time period, plateauing after 2009 and followed by a modest decline in 2013 to 8.3%; however, the rate rose again to 8.6% in 2014.

Parents are often told that their children will likely grow out of asthma, but according to a recent study by Andersson and colleagues, this may occur in only 21% of patients; women, severe asthmatics, and those with animal allergies have the lowest remission rates. Thus, since the majority of asthma patients do not have full resolution in their lifetime, more focus should be on preventive measures that are simple and noninvasive. Evidence shows that the most opportune times for preventive treatments are the prenatal and perinatal periods, through modification of diet and lifestyle factors.

THE MICROBIOME
The microbiome has received considerable attention in medical communities in recent years, reflected by a large volume of published research on the subject. The intestinal flora plays a substantial role in directing immune system development in infants, including but not limited to improved thymus development and antibody response to vaccination. The intestinal milieu is an integral factor in asthma development through several mechanisms, including mucosal immunity, production of immunoglobulins E (IgE) and A (IgA), and modulation of allergic reactions to antigens. Lactic acid–forming
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bacteria specifically induce production of interleukin-10 (IL-10),
22 an anti-inflammatory mediator, illustrating their role in asthma prevention. Interestingly, this is also a mechanism of corticosteroid therapy for alleviating asthma symptoms.23,24

Disrupting the internal microbial environment of pregnant women often results in increased asthma risk in their offspring. A study of 39,907 mothers in China revealed that treatment of mothers with either penicillin or chloramphenicol during pregnancy was associated with childhood asthma in their children, especially if treatment occurred during the first trimester.25 Metsala in Sweden showed that prenatal cephalosporin exposure, as well as infant exposure during the first year to cephalosporins, sulfonamides, trimethoprim, macrolides, and amoxicillin, was associated with an increased risk of asthma.26 Postnatal antibiotic exposure in infants seems to have similar effects in other areas of atopy; in a Swedish birth cohort of 4,051 children, antibiotic intake in the first year of life increased allergic rhinitis risk, while living on a farm decreased the risk.27 These findings are consistent with the hygiene hypothesis. However, another recent study questioned whether some of the data supporting the hygiene hypothesis is due to reverse causation. The correlation of asthma and antibiotic use during fetal and early life was only shown when antibiotics were used for respiratory infections and not for urinary tract or skin infections.28 Frequent respiratory infections are a known risk factor for asthma development. An earlier large meta-analysis of 21 research articles showed that probiotic administration during fetal and early life did not decrease asthma risk but did decrease atopic sensitization risk and total IgE levels in children.29 It is important to note here that studies showing an insignificant influence of probiotics on the development of asthma or atopy may be due to the limitations of investigating single-strain effects; measuring total microbial diversity and quantity seems to be a more reliable technique for determining the influence of the microbiome on the development of atopy.30,31

VITAMIN D: PRENATAL AND POSTNATAL
Like the microbiome, vitamin D has garnered consideration for its role in many conditions that have inflammation as a vital part of their pathophysiology. Vitamin D deficiency [defined as 25-hydroxyvitamin D (25-OH vitamin D) level <20 ng/mL] during pregnancy can have significant inverse effects on asthma development and lung function.32 A 2014 study by Zosky showed that prenatal deficiency of vitamin D was related to increased asthma incidence at 6 years of age in boys, while girls showed a decrease in forced expiratory volume (FEV). When data was collected again at 14 years, girls whose mothers were vitamin D–deficient in pregnancy had adversely impacted FEV1/FVC (forced vital capacity) ratios. This pattern reflects existing data on asthma rates by gender, which show that males younger than 18 years have a 16% higher asthma rate than females the same age.33 Interestingly, several studies show gender differences with respect to lung development and asthma. In animal models, males have a stronger immune response when exposed to allergens, with higher rates of both eosinophil and neutrophil production compared to females.34 In humans and animals, there are also gender disparities in lung surfactant production, occurring earlier in female neonates than male.35 Vitamin D is intricately involved with maturation of the surfactant system.36 These influences of prenatal deficiency on asthma and lung function may be strongest if the mother is deficient between 16 and 20 weeks gestation, a time period when the majority of lung cell differentiation occurs.37 Furthermore, concerns have been expressed over earlier findings that supplementation in late pregnancy may increase childhood asthma and eczema risk,38 but more recent research did not demonstrate any significant associations with development of any atopic conditions, including asthma.39

After birth, vitamin D supplementation in the infant can also play a critical role in asthma prevention and treatment. In the first in vivo study on vitamin D and its relationship to lung function and structural changes, Gupta et al discovered that children with moderate and steroid-resistant asthma were affected significantly by their vitamin D levels; asthma exacerbations and steroid use were inversely related to vitamin D serum concentrations.40 Airway smooth muscle mass was also increased with lower vitamin D levels, but only in the steroid-resistant asthmatics in that study. This increase in mass may be a result of chronic inflammation, a phenomenon also seen (continued on page 10)
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in those with chronic allergic rhinitis and subsequent turbinate hypertrophy. Gupta et al additionally reported a direct relationship between vitamin D levels and positive performance on the Asthma Control Test, a self-administered tool for identifying patients 4 to 11 years old with poorly controlled asthma.\textsuperscript{41} Reverse causation should also be considered; multiple studies show that vitamin D levels can be depressed as a result of systemic inflammation for up to 3 months afterwards.\textsuperscript{42-44}

In 2008, the American Academy of Pediatrics (AAP) published guidelines for infant vitamin D intake at 400 IU daily,\textsuperscript{45} in order to maintain 25-OH vitamin D levels >20 ng/mL.\textsuperscript{46} However, the recommended daily intake for infants of 400 IU as stated in 2011 by the Institute of Medicine reveals that this would maintain a 25-OH vitamin D level of only 16 to 20 ng/mL.\textsuperscript{47} Considering that levels less than 20 ng/mL represent deficiency, and 20 to 32 ng/mL represents insufficiency,\textsuperscript{48,49,50} these recommendations will likely be inadequate for achieving necessary concentrations for many people. The AAP recommendations for breast-fed infants include continuation of supplementation unless an infant is additionally consuming at least 1 liter per day of vitamin D–fortified formula or 1 quart per day of fortified whole milk.\textsuperscript{47} Concerns expressed about vitamin D toxicity may be overestimated, as daily supplementation in infants up to 1,600 IU per day does not appear to result in hypercalcemia.\textsuperscript{51-54} The standard recommendation for vitamin D intake during pregnancy is 400 to 600 IU per day. However, in the first study that tested the current prenatal upper limit of 4,000 IU per day, this dose produced sufficient levels in both the mother and neonate without any adverse effects, while the standard recommendation of 400 to 600 IU per day did not.\textsuperscript{55} Therefore, this author proposes that vitamin D intake guidelines should be revisited, at least for pregnant and breast-feeding women as well as infants.

Inverse relationships have been reported between vitamin D concentration and IgE levels, eosinophil count, hospitalizations for asthma, lung function, and use of asthma medications such as ICS and leukotriene inhibitors.\textsuperscript{56-58} Furthermore, Goleva et al found inverse relationships between vitamin D levels and both ICS use and IgE levels in asthma.\textsuperscript{59} Searing et al had similar findings and also discovered that vitamin D in vitro increased corticosteroid effectiveness, evidenced by enhanced IL-10 production by CD4+ T cells.\textsuperscript{50} Previously, Xystrakis et al found that CD4+ T cells of steroid-resistant asthmatics were unresponsive to dexamethasone by not producing IL-10, whereas cells from steroid-sensitive asthmatics did produce IL-10. Subsequently adding vitamin D to these steroid-resistant cells enhanced dexamethasone effectiveness by increasing IL-10 production to levels seen in steroid-sensitive cells.\textsuperscript{61} It has been postulated that corticosteroid upregulation of renal 25-hydroxyvitamin D(3)-24-hydroxylase activity, which degrades vitamin D metabolites, is the mechanism responsible for reduced vitamin D levels in patients taking ICS.\textsuperscript{62,63} Vitamin D supplementation also attenuated the severity of atopic dermatitis, often a precursor to asthma, by regulating the balance of type 1 and type 2 T helper (Th1 and Th2) cells,\textsuperscript{64} which is skewed in asthmatics as well.

**DIETARY AVOIDANCE**

The effect of maternal diet during breastfeeding on atopic development has been extensively studied, with conflicting results. A study of primarily atopic mothers found that maternal cow’s milk avoidance while breast-feeding may increase risk of cow’s milk allergy in the infant.\textsuperscript{65} Avoidance in study participants resulted in lower cow’s milk–specific IgA in their breast milk. Subsequently, those infants who did develop cow’s milk allergy had much lower casein-specific IgA compared to control infants, as well as lower beta-lactoglobulin–specific and casein-specific IgG4 levels. The researchers demonstrated that breast milk low in cow’s milk–specific IgA reduced the antigen trafficking in vitro. The presence of secretory IgA would otherwise decrease this trafficking and therefore reduce immune system exposure to those allergens at the mucosal barrier.\textsuperscript{66} Considering that most of the mothers and siblings of the infants in this study were atopic, more research is needed to determine whether these findings are applicable to the general population. Other research has confirmed that limiting the diet of a pregnant mother or a breastfeeding mother as well as the infant may not decrease risk of atopy or food-related allergies such as wheat and egg.\textsuperscript{67,68}
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EMOTIONS AND ASTHMA
The emotional link to asthma exists on several levels. Consistent feelings of shortness of breath or even the anticipation of an exacerbation can induce anxiety and depression, commonly occurring comorbidities found in asthmatics as well as patients with chronic disease. To compound this scenario, chronic stress is a known precursor to decreased lung function as well as the fraction of exhaled nitric oxide, a marker for airway inflammation. As mentioned previously, asthma treatments such as montelukast may increase the risk for depression, and those with major depressive disorder show elevations in pro-inflammatory cytokines such as IL-6 and inflammatory marker C-reactive protein were not due to another existing condition. Interleukin-6 and tumor necrosis factor (TNF)-alpha are commonly elevated in asthmatics and are also associated with symptoms of depression. This association may be explained through several factors; TNF-alpha can affect serotonin metabolism by activating indoleamine 2,3-dioxygenase, leading to a peripheral tryptophan depletion. Therefore supplementation may be of benefit and IL-1, IL-6, and TNF-alpha, pro-inflammatory mediators abundant in asthmatics, can stimulate hypothalamic-pituitary-adrenal (HPA) axis activity, as does acute stress. Conversely, an overactive HPA axis may be due to reduced sensitivity to endogenous (cortisol) and exogenous corticosteroids and thus the negative feedback they provide. One of the consequences of this blunted immune-suppressive action is higher TNF-alpha production demonstrated in asthma patients. This decreased response to corticosteroids has been identified in depressed patients as well.

OXIDATIVE STRESS
Increased oxidative stress plays a significant role and is a common finding in asthma. In fact, exhaled volatile organic compounds (VOCs), a marker of lipid peroxidation induced by reactive oxygen species, can help predict asthma exacerbations in children. During the inflammatory process, immune cells release reactive oxygen species that further increase the inflammatory response. In animal models exposed to allergens, S-adenosylmethionine treatment decreased airway inflammation through suppression of pro-inflammatory cytokines, likely by reducing oxidative stress through its participation in the methylation cycle. Relatedly, reduced eosinophil methylation activity was seen in asthma patients with high IgE levels, and to a lesser extent asthmatics without elevated IgE levels, when compared to controls. Another consideration is that reactive oxygen species can impair mitochondrial function, which can further reduce their ability to prevent oxidative stress, leading to airway inflammation, smooth muscle remodeling, and increased smooth muscle mass seen in both chronic obstructive pulmonary disease (COPD) and asthma. Other findings show that asthma symptoms were inversely related to serum selenium concentrations and directly associated with glutathione reductase activity in men. Guo et al additionally found that an antioxidant vitamin supplement can also attenuate oxidative stress and hence improve asthma control scores.

CONCLUSION
The existing volume of research on many aspects of asthma pathogenesis exposes the obvious connections between them. The use of pharmaceutical medication as the only approach to treat asthma has revealed that it is simply not sustainable. Without considering the measures stated here, we can expect asthma rates to remain unchanged or, more likely, to increase. Nevertheless, it is clear that asthma medications are necessary for the safe treatment of patients with asthma. However, stressing the importance of diet, vitamin D supplementation, the microbiome, and emotions in all stages of life could diminish the tempest that is asthma and potentiate the change all physicians hope to see for this condition.

REFERENCES

(continued on page 14)
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Efficacy of Probiotics for Infant Colic: A Discussion with Probiotic Expert Ashton Harper, MBBS, MRCS

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In this interview, Ashton Harper, MBBS, MRCS, describes the research associated with probiotics to help prevent and treat a variety of conditions in children. He also describes a new study using probiotics to treat infant colic and explains why it’s so important to treat colic as soon as it’s diagnosed.

ABOUT THE EXPERT
ASHTON HARPER, MBBS, MRCS, has a bachelor of science degree in physiology and pharmacology from University College London (UCL). He graduated with a degree in medicine (MBBS) from UCL in 2010. He worked in the National Health Service for 5 years, during which time he discovered his passion for the management of gastrointestinal diseases. While working in gastrointestinal surgery he achieved membership of the Royal College of Surgeons and was awarded a post-graduate travelling fellowship to visit the Cleveland Clinic to observe world-leading doctors manage inflammatory bowel disease. He has published in the fields of nutrition and gastrointestinal diseases and has presented his work at multiple national and international medical congresses. Harper is a medical advisor for the Protexin Human Healthcare team, where he is responsible for providing medical expertise for the business.

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Usable Green Spaces Can Affect Children’s Health-Related Quality of Life and BMI

Evidence supports the benefits of the great outdoors

By Kurt Beil, ND, LAc, MPH

ABSTRACT & COMMENTARY

PRACTICE IMPLICATIONS

This is one of the first studies in the growing body of green space and health literature to use children as a population of interest. Children are a critical population to consider, and not only because of the epidemic of childhood obesity that is currently plaguing our healthcare system with physical and mental health effects. It is also vital that children be exposed to nature as early as possible to instill an ethic of environmental stewardship; studies have shown that children who don’t get this exposure are less creative, less empathetic, and less likely to care about the environment as adults. In this era of “screen time vs green time,” there is growing concern that the next generation will not be able to provide enough capable, eco-minded leaders to solve the massive environment-related health problems that are coming our way.

In addition, this study is one of the first to use a broad measure of health rather than investigating a specific biomarker or pathologic condition. HRQOL is an important metric in healthcare because it focuses on qualitative aspects of well-being rather than traditional quantitative metrics like disease prevalence or mortality rates. It also assesses the holistic, “multidimensional” aspects of life and considers how health affects all aspects of life. It is useful to remember that “health” itself is a holistic condition as defined by the World Health Organization (WHO). According to WHO, health is “a state of physical, mental, and social well-being and not merely the absence of disease or infirmity...[Health is] a resource for everyday life, not the objective of living...[Health is] a positive concept emphasizing social and personal resources, as well as physical capacities.”

In an era in which so much of the medical system takes a pathocentric (disease-focused) approach to healthcare, it is nice to know that some interventions do have a salutogenic (health-promoting) effect. For the practitioner, this study emphasizes that environmental factors may act as enhancers or barriers to achieving health. There are many things in a patient’s
The positive associations between activity level and quality of life and negative associations between hours of TV and quality of life demonstrate how vital it is to encourage movement and decrease sedentary behavior in children. These findings also suggest the value of taking a proactive approach to getting kids outside. The positive associations between activity level and quality of life and negative associations between hours of TV and quality of life demonstrate how vital it is to encourage movement and decrease sedentary behavior in children. Increasingly, more conventional physicians are organizing and creating standardized “Vitamin N” (for “nature”) prescription-writing programs. Under the umbrella program of ParkRx in conjunction with the National Park Service, the National Recreation and Park Association, and the Institute at the Golden Gate, doctors are learning their role in promoting children’s use of the “natural medicine” a nearby park can provide.

REFERENCES
Parental Sleep and Reported Sleep Quality of Children

Intervention for sleep problems should address the entire family unit

**REFERENCE**

**DESIGN**
A cross-sectional, observational study

**OBJECTIVE**
To assess the association of parental sleep quality with the reported sleep quality of their children

**PARTICIPANTS**
In this study, parents and their biological children aged 2 to 6 years were recruited from 16 daycare centers in Finland. A total of 108 children were enrolled and evaluated between January 2014 and February 2015. The mean age of the children was 4 years and the sex distribution was even. The sample included mainly Caucasian, highly educated families.

**OUTCOME MEASURES**
Parents completed questionnaires regarding socioeconomic status, their own well-being, and their child’s well-being and illnesses.

An actigraphy bracelet was provided for the child to wear on their nondominant hand for a period of 7 days. Parents were instructed to press the event button on the bracelet when the child went to sleep and when they woke up. While the actigraph does not differentiate between stages of sleep, it does estimate periods of sleep using a threshold for lack of movement. With consideration for the restless nature of children’s sleep, studies indicate that the actigraph shows good sensitivity (the ability to detect sleep), but poorer specificity (the ability to detect wake) in pediatric populations. However, the authors note that the accuracy can be enhanced using an appropriate algorithm.

Parents kept a sleep diary for the duration of the time that the child wore the actigraphy bracelet, which included the details of when and why the actigraphy bracelet was removed during this period.

Along with the sleep diaries, parents also completed the Sleep Disturbance Scale for Children (SDSC) which, in addition to the total score, evaluates 6 different sleep domains: disorders of initiating and maintaining sleep; sleep breathing disorders; disorders of arousal; sleep-wake transition disorders; disorders of excessive somnolence; and sleep hyperhidrosis.

With respect to their own health, parents completed both the Jenkins’ sleep scale and a 12-item General Health Questionnaire in order to assess parental sleep quality as well parental psychiatric symptoms, including anxiety and depression.

**KEY FINDINGS**
The authors found that parents who reported having sleep difficulties themselves were more likely to experience their children as having more sleep difficulties. Furthermore, they found that this association was not supported by the study’s objective measure, the actigraph, indicating that the child’s sleep may not actually be as poor as parents perceived. The perception of children’s sleep difficulties was not explained by the child’s age, sex, number of siblings, chronic illness, or medication, nor was it related to parental psychiatric symptoms, education, socioeconomic status, marital status, or time of year.

**COMMENTARY**
Many factors influence children’s sleep, including social and cultural environments, parental knowledge, and the child’s pre-existing medical conditions. Poor sleep and sleep disorders can have detrimental effects on a child’s anxiety level, mood, behavior, physical development, and weight, as well as academic competence. Thus, there is a need for screening and early intervention in sleep disorders. However, sleep screening and intervention may not be occurring as frequently and as effectively as one would hope.

Large epidemiological studies reveal that approximately 30% of children suffer from sleep problems. Despite this prevalence, the rates of screening and management of these concerns are low. Both primary care providers and parents frequently have gaps in knowledge when it comes to the topic of sleep in the pediatric population.

Children depend on their parents’ understanding of their sleep needs in order to foster a healthy sleep regimen that is developmentally appropriate. In turn, parents rely on their healthcare providers to inquire about a child’s sleep habits routinely, identify problems, and provide education on the subject. Parental education is often the first line of intervention, and increasingly clinicians are recognizing that parental knowledge impacts child sleep behavior. However, primary care providers receive minimal training...
about sleep. This may result in missed opportunities for discussion during visits, unless parents are reporting problems or asking questions pertaining to sleep.\(^3\)

Studies indicate that sleep disorders are more prevalent in single-parent families, and/or those with low parent education. This means there is more need for practitioner inquiry and education in patient visits where these conditions exist.\(^4\)

When assessing sleep, there are 4 dimensions to consider: amount, quality, timing, and state of mind. BEARS is a useful acronym to use when asking parents and care providers about children’s sleep: (B) bedtime resistance (sleep onset delay); (E) excessive daytime sleepiness; (A) awakening at night (parasomnias); (R) regularity, patterns, and duration; and (S) snoring and other symptoms.\(^4,6\)

The authors found that parents who reported having sleep difficulties themselves were more likely to experience their children as having more sleep difficulties.

While there are many pediatric sleep disturbances, among the most common is pediatric insomnia, which affects approximately 6% of typical children and as many as 75% of children with developmental impairments. In cases of pediatric insomnia, it is frequently the parent rather than the child who is frustrated, and the parent is often the one experiencing negative effects on daytime performance and increased stress levels.\(^5\)

It is easy to see how, especially in cases such as these, parental emotions may influence prescribing behaviors of providers. The National Ambulatory Medical Care Survey demonstrated that, in visits involving sleep difficulties, 81% of children leave with a prescription compared to 48% of adults. What is particularly concerning about this statistic is that there are currently no medications on the market that are FDA-approved for treating sleep problems in children.\(^6\) While integrative practitioners would be unlikely to suggest prescription sleep aids, it would be interesting to know whether a similar percentage would give children homeopathic, botanical, or nutritional supplements for sleep. Of course, when multiple behavioral interventions fail, both naturopathic and prescription treatments may be appropriate; however, a sedated sleep does not equate with a normal restorative sleep.\(^7\)

As a naturopathic doctor, this study reminds me of 2 core principles we uphold: *tolle causam* (find the cause) and *docere* (teach). In addition, the therapeutic order for all patients is to remove disturbing factors and institute a healthful regime before interventions of any kind. In cases of pediatric sleep concerns, we should be addressing the entire family unit and ensuring that there are no unnecessary interventions, that carry the possibility of harm. We must consider that parents may be over-reporting their children’s sleep disturbances because of their own sleep disorders. In addition to this, we must discuss the expectations that parents and caregivers have for their children’s sleep, in comparison with the developmental norms for their respective age groups. This leads to a natural segue to provide education surrounding these norms, including sleep requirements and good habits, understanding the signs of sleep problems, and suggestions on how to improve sleep for the whole family.

Parents with greater knowledge about sleep are more likely to establish better sleep hygiene routines for their children, including a regular, early bedtime, regular wake times, falling asleep without an adult, and no TV in the bedtime routine.\(^3\)

Instead of simply relying solely on parental reporting of sleep disturbances and immediately treating children with sedative, nervine, and adaptogenic botanicals, or supplements such as melatonin, it may have a greater impact on the family unit to assess and treat the parents’ sleep. Addressing healthy sleep hygiene with the whole family will only have a positive impact. While parents generally recognize the importance of

\(^{1,2}\)
a bedtime routine for their children, we may need to remind them that an established routine is essential for their sleep and health as well.

Further studies on preconception and perinatal sleep habits and sleep quality of parents may also prove to be of interest. While the assumption is that parents who were sleeping poorly in the preconception and perinatal periods are over-reporting sleep disturbances in their children, it is equally possible that parents who were good sleepers before they had children are the ones who have poorer sleep after having children. These “good sleepers” may feel more “interrupted” compared to parents who were already used to poorer quality sleep. This is an unknown, and further research is warranted to investigate whether children with sleep disturbances have parents with historically poor sleep or good sleep. This may also inform us about whether sleep disturbances are influenced by genetic or learned behaviors.

REFERENCES
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Iron Supplementation in Pregnancy and Infancy

Iron sufficiency is critical for optimal development

By Lilian Au, ND

REFERENCE

OBJECTIVE
To assess the effects of iron supplementation in pregnancy and/or infancy on motor development at 9 months

DESIGN
The study was a randomized controlled trial (RCT) of iron supplementation in early infancy; the results were linked to an RCT of prenatal iron supplementation (conducted in Hebei, China) to compare effects of prenatal vs postnatal supplementation.

PARTICIPANTS
The studies included a total of 2,371 women with single uncomplicated pregnancies and 1,482 infants. Infants were randomly assigned to receive either supplemental iron (n=752) or placebo (n=730) from 6 weeks to 9 months. Maternal and infant iron status and infant growth outcomes were considered in the criteria. The infants with cord ferritin levels suggesting brain iron deficiency (<35 ug/L) were excluded from the study. Developmental testing for the infants at 9 months occurred at the Peking University Maternity and Child Health Care Center.

OUTCOME MEASURES
Investigators used the Peabody Developmental Motor Scale to assess gross motor development (primary outcome) and neurologic integrity and motor quality (secondary outcomes).

KEY FINDINGS
The authors compared the effects of iron/folate supplementation for prenatal patients and iron supplementation for infants from ages 6 weeks to 9 months. Iron supplementation in infancy, with or without iron supplementation in pregnancy, improved gross motor test scores at 9 months. There was improvement in gross motor scores: overall, \( P<0.001 \); reflexes, \( P=0.03 \); stationary, \( P<0.001 \); and locomotion, \( P<0.001 \). Iron supplementation in infancy improved motor scores by 0.3 SD compared with no supplementation or supplementation during pregnancy alone.

PRACTICE IMPLICATIONS
This study is one of many to show how the benefits of iron supplementation during early infancy can affect the developmental outcomes of growing infants. Overall, there was a positive effect on gross motor and neurological development for the infants supplemented with iron from early infancy as well as infants whose mothers received supplementation during pregnancy. Thus, this study confirms the importance of supporting potential nutritional deficiencies in early infancy—the period of most rapid growth and changes in motor development.\(^1\)

The study supports the assertion that iron supplementation during infancy significantly improves gross motor skills during a child’s first year of life. The infants receiving iron supplementation during this rapid period of growth performed better on developmental milestones such as sitting upright, crawling, standing with lateral progression, and transitions from sitting to standing than the group who received no supplementation. Existing research shows a strong connection between iron deficiency and a child’s cognitive, social-emotional, and gross and fine motor development.\(^2\) In these studies, iron-deficient infants exhibited slower progression, delayed milestones, withdrawal, and lower spontaneous activity. Because areas of the brain mature at different times, it is critical to initiate iron supplementation during the earliest developmental periods and consider prenatal support as well.\(^3\)

Iron deficiency is the most prevalent nutritional deficiency in the late infancy/toddler period.\(^4\) Notably, the study period focused on the specific ages (between 6 weeks and 9 months) when an infant’s brain matures most rapidly and iron is needed most in the formation of the brain’s neural network. The significant growth of the complex brain areas within the first year of life relies on iron and is most vulnerable to iron deficiencies or insufficiencies through the breast milk, diet, or during growth and development in the perinatal period.\(^5\) Periods of peak development and metabolic activity in the brain are sensitive to substrates that support metabolism, such as iron and thyroid hormone. This time period is characterized by peak hippocampal and cortical regional development, as well as proper myelin and synapse formation and oligodendrocyte function in the brain.

Recent studies have shown a relationship between perinatal iron deficiency and negative effects on the developing hippocampus in infants as young as 2 months. Infants who showed consistent and sufficient iron levels had greater auditory recognition memory when compared
to infants who had fetal-neonatal iron deficiency. Results from a 2016 study of iron deficiency and its effects on thyroid development and function in neonates (Hu et al) support the strong relationship between maternal iron levels and thyroid peroxidase synthesis, which is key to neonatal neurodevelopment because it depends so heavily on healthy perinatal iron levels and optimal thyroid function. Iron deficiency has a direct effect on sensory input which, combined with cognitive, motor, and affective changes, may adversely affect the infant’s interactions with the physical and social environment. Treating and resolving iron deficiencies in early infancy and childhood has been shown to decrease the likelihood of long-lasting neural and behavioral effects.

Insufficient iron levels for optimal fetal and infant development are a concern during pregnancy and infancy with lasting effects into childhood. Despite the results of this study on iron supplementation in the prenatal period and its effect on motor development in infancy, other research shows a solid connection between the mother’s dietary and nutritional status during fetal development and the child’s overall growth and development. Although this current study of pregnant women in China did not show greater benefits in the child’s motor development with the addition of iron and folate supplementation, it is still important to support the critical nutritional needs for both mother and child.

Previous trials in China exploring prenatal iron supplementation and its effects on both mother and child found that supplementation had a positive response in reducing anemia overall, but iron deficiency still exists in more than 45% of children and about 70% of mothers despite supplementation. In contrast, a study of prenatal iron supplementation in pregnant women in the United States revealed that only about 18% of women who did not receive supplementation experienced iron deficiency. Therefore, we should consider other factors that may account for the results of studies from rural China, such as whether or not poor nutrition or environmental toxicities can affect the study participants in the long term. For example, deficiencies of essential nutrients, such as iron, calcium, and zinc, may increase the absorption of lead. These nutritional deficiencies are likely to be more prevalent in vulnerable groups such as low-income or minority populations. According to the study by Jain et al on lead intoxication, there is considerable research regarding the effects of lead toxicity on iron absorption and iron-deficiency anemia. Thus, the research supports the importance of supplementing iron for women in China during the prenatal period and preventing the deficiencies in early infancy and childhood.

Overall, the results of this study from Angulo-Barroso et al confirm the developmental benefits of iron supplementation early in infancy and indicate that supplementation should be an important part of routine care for all infants and mothers, especially those with demonstrated iron deficiency, as well as populations at risk for malnutrition and nutritional deficiencies.

REFERENCES
ABSTRACT & COMMENTARY

IBS and Probiotic Treatment in Pediatric Patients
Effects of Lactobacillus rhamnosus GG on pain and function

By Paul Richard Saunders, PhD, ND, DHANP

REFERENCE

DESIGN
Randomized, double-blind, placebo-controlled trial

PARTICIPANTS
Fifty-two children, 4-18 years old (25 female, 27 male) all had active abdominal pain for at least 2 weeks before entering the study. All participants were diagnosed by a pediatric gastroenterologist using Rome III Criteria for irritable bowel syndrome (IBS) with other differential diagnoses excluded by laboratory, abdominal ultrasound, radiographic imaging, endoscopy, and hydrogen breath test as required. Exclusion criteria included any medication use and any underlying diseases

OUTCOME MEASURES
Severity of pain; functional changes (eg, disruption of social activities, need to see a doctor; use of medications, days absent from school); and variables that could induce abdominal pain (eg, gastroenteritis, abdominal pathologies, life events) were primary outcomes. A validated scale (Likert scale) was used to specify severity of the pain from 0 to 5, with 5 being most severe. A 3-point Likert scale was used to assess function changes (1-decrease, 2-no change, 3-increase). Secondary outcomes were changes of the functional scale, stool patterns, and associated problems (eg, headache, limb pain, sleep problems).

INTERVENTION
Lactobacillus rhamnosus GG at 1x10^10 CFU/mL or placebo of inulin (also in treatment capsule), 1 capsule twice daily for 4 weeks. Capsules were the same size, color, and taste.

RESULTS
There were 52 evaluable participants at the study conclusion. Of the 60 initial participants, none discontinued due to reaction to treatment or placebo. The mean age of the children evaluated was 7.1 years old. Their most common type of IBS was alternating constipation and diarrhea, experienced by 16 children in the placebo group and 15 in the treatment group. Of the remainder, 6 in the placebo group and 6 in the treatment group had mostly constipation, and 4 in the placebo group and 6 in the treatment group had mostly diarrhea.

Pain severity decreased significantly in the treatment group versus the placebo group after 1, 2, 3, and 4 weeks of treatment (P=0.01, 0.00, 0.00, 0.00, respectively). There was significant improvement in the functional scale after 2 weeks in the treatment group (P≤0.00). There was no significant change in stool consistency or associated problems over the 4 weeks (P>0.1).

FINDINGS
This study demonstrated that Lactobacillus GG 1x10^10 CFU/mL twice daily can significantly reduce pain in pediatric IBS after 1 week and improve functional ability after 2 weeks, but the probiotic had no significant effect on stool consistency or associated health problems at the end of 4 weeks.

COMMENTARY
This was a well-designed study, but the lack of reporting all outcome measures as well as the statistical analysis weakened it considerably. The functional Liker scale was not presented, so that data is not available to evaluate. The significant P values reported as 0.00 are either errors, typos, or otherwise incorrect. The lack of significant change in stool habit is disappointing but not uncommon in IBS studies. The short length of this study may be a factor; in clinical, practice stool consistency changes can occur over the long-term.

Lactobacillus rhamnosus is naturally found in the gastrointestinal tract and the healthy female genitourinary tract. It also is used in yogurt and other fermented dairy, as well as semi-hard cheeses. Sherwood Gorbach and Barry Goldin isolated this species in 1983 from the intestinal tract of a healthy human. They sought a beneficial bacteria that would colonize, survive an acid environment, and out-compete pathogenic bacteria. On April 17, 1985, they filed for a patent of Lactobacillus acidophilus GG (from the first letter of their surnames) as ATCC 53103 (American Type Culture Collection). It was later reclassified as Lactobacillus rhamnosus GG (ATCC 53103). It is considered the world’s most studied probiotic bacteria. It can survive the acid and bile of the stomach and small intestine to colonize the digestive tract, stop peanut allergic reactions in most children, prevent rotavirus diarrhea in children, and reduce abdominal pain in children. It also has the potential to stop respiratory tract infections in children at daycare.
Russian Nobel laureate Ilya Ilyich (Elie) Metchnikoff, professor at the Pasteur Institute in Paris, proposed in 1906 that one could modify the gut flora, replacing harmful bacteria with beneficial bacteria. He further proposed that the aging process resulted from the activity of putrefactive or proteolytic bacteria that produced toxins in the large bowel. The compound produced by this activity caused autointoxication and the physical changes associated with aging. His work sparked both controversy and research into the role of gut microbes and human health.

The controversy surrounding probiotics and their clinical effects is closely tied to the diverse species tested and the dosage used. A medium-size study (N=362) of encapsulated *Bifidobacterium infantis* 35624 compared 1x10^6, 1x10^8, 1x10^10 CFU/mL in women with IBS over 4 weeks. The middle dose, 1x10^8, was significantly effective for abdominal pain, bloating, bowel dysfunction, incomplete evacuation, straining, and flatulence reduction. The other 2 doses were no better than placebo, and the largest dose had formulation issues. No adverse events were recorded. The authors concluded that the dose and dosage form were features of probiotic use that still needed clinical data and resolution.

A study of 141 children with IBS in 9 centers over 8 weeks used *Lactobacillus rhamnosus* GG or placebo for pain control. There was significant reduction in pain frequency (P<0.01) and pain intensity (P<0.01). These results were still significant at 12 weeks. When the trial began, 59% of the children had abnormal intestinal permeability. At the end of the trial the treatment group had a significant reduction (P<0.03) in intestinal permeability.

Study finds *Lactobacillus rhamnosus* GG significantly reduces pain severity after one week and significantly improves functional ability after two weeks in children 4 to 18 years old.

Some studies show increased short-chain fatty acids that coincide with increased lactic acid bacteria and/or *Bifidobacterium* species. Supplementation with *Bifidobacterium* can directly stimulate butyrate producers that utilize acetate or lactate. Decreased butyrate production and the subsequent bloom of proteobacteria is associated with IBS, inflammatory bowel disease (IBD), and type 2 diabetes.

There is a need for studies that identify specific probiotic-induced changes in the gut. Giving *Lactobacillus rhamnosus* GG, and *L Casei* Shirota can increase *Bifidobacterium* populations. Administration of 1x10^9 CFU/mL *Lactobacillus rhamnosus* GG from birth to 6 month increased *Lactobacillaceae* and *Bifidobacteriaceae*. It also resulted in more community “evenness,” a greater diversity of species, and less risk of developing allergic disease. Starting with a healthier bowel may reduce the risk for IBS, IBD, and other microbial dysbiotic conditions.

A current review article argues that since up to 50% of orally ingested strains survive gastric passage, ingested bacteria can impact resident communities by trophic interactions such as competition for substrate; a direct alteration of fitness (eg, competitive exclusion, physical displacement, vitamin production); or an indirect alteration of fitness (eg, altered production of host-derived molecules, bile salt alteration). Alteration of bile salts determines the fitness of the bowel, the expression of some bacteria, and the risk for some diseases.
CLINICAL IMPLICATIONS

*Lactobacillus rhamnosus* GG has been shown in a randomized, double-blind, placebo-controlled clinical trial to lessen abdominal pain and improve functional ability in children 4 to 18 years old with Rome III–defined IBS. The dose was $1 \times 10^{10}$ CFU/mL twice daily. The unknowns for clinicians are how the subjects’ gut microbes were altered to achieve this effect and how *L. rhamnosus* GG compares to other probiotic species or species combinations. The unfortunate finding is the lack of change in stool consistency at the end of the 4-week trial. Given the risk/benefit analysis easily tips the scale in favor of the intervention, it may only be through time and trial that clinicians learn if this treatment warrants endorsement.

REFERENCES

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REFERENCES

DESIGN
This parallel clinical trial was a randomized, triple-blind, placebo-controlled study. It was conducted between April 2009 and March 2010.

PARTICIPANTS
Study included 600 children (ages 1-5 years) from the Brazilian Public Health System in Petropolis (BPHSP), Rio de Janeiro. The inclusion criteria were: male or female patients with no apparent disease. Children who lived in geographical areas that were difficult to monitor and those with the following characteristics were excluded: history of wheezing and asthma, HIV infection, immunodeficiency, type 1 diabetes, malignancies, corticosteroid treatment, congenital anomalies, liver disease, history of at least 1 episode of respiratory infection in the previous 30 days.

STUDY MEDICATION AND DOSAGE
The children were randomized into 3 intervention groups with 200 patients in each group: homeopathic complex, placebo, and InfluBio.

The InfluBio solution was prepared by serially diluting a sample of purified influenza virus [A/Victoria/3/75 (H3N2)] in 1:10 ratio with sterile water to a 30x dilution according to the Brazilian Homeopathic Pharmacopea employing mechanical succession 100 times between each dilution.

The homeopathic complex used was composed of bacterial strains (Streptococcus and Staphylococcus) and inactivated influenza virus, prepared following the same homeopathic procedures of serial dilution and succession to a 30x dilution. This medicine is used routinely in Brazil for the prophylaxis and treatment of upper respiratory tract infections. The placebo consisted of 30% alcohol in a sterile water solution, which was the same composition used to dilute the homeopathic agents prepared in this study.

The child’s tutor administered the test solutions twice a day for 30 days.

During the study, neither the families nor the healthcare providers knew which solution was being given to each child.

OUTCOME MEASURES
The number of episodes of flu and acute respiratory infection during a 1-year period, as well as the duration of flu or acute respiratory infection, was tracked using a standardized questionnaire.

To characterize the number of flu and acute respiratory infection episodes, at least 2 of the following symptoms had to be present: fever (temperature > 37.8°C), nasal discharge, prostration, myalgia, headache, and cough.

KEY FINDINGS
Of the 600 children selected, 445 (74.17%) children completed the study (149: homeopathic complex; 151: placebo; 145: InfluBio) and 155 (25.83%) children dropped out during the research period. Of the children who completed the entire study period, the mean age was 2.4 years without differences among groups.

Most of the children were classified as Caucasian or mixed-race living in the urban area. In the year before the study, most children had at least 1 episode of either flu or acute respiratory infection. In general, the number of flu and acute respiratory infections detected was low. The incidence of flu and acute respiratory infection episodes in the group that received placebo was higher compared to the groups that received homeopathic medications. The difference between homeopathic and placebo groups was statistically significant (P<0.001), whereas the difference between the homeopathic medicine groups was not (P=0.99).

In the first year post-intervention, 46 of 151 children (30.5%) in the placebo group developed 3 or more flu and acute respiratory infection episodes, while there was no episode out of 149 children who used homeopathic complex and only 1 out of 145 (1%) in children who received InfluBio.

PRACTICE IMPLICATIONS
The results reported by Siqueira et al in this paper are incredible, but as in the true meaning of the word, unbelievable. They seem just too good to be true.

Our belief as naturopathic physicians in the efficacy of homeopathic medicines in which the active agent employed has been diluted to the point of extinction contradicts logic and generally accepted scientific understanding. Despite the logic-defying premise of homeopathy, experience of apparent clinical efficacy (continued on page 32)
RECOMMENDED TO SUPPORT:
• BALANCED BEHAVIOR AND SOCIALIZATION SKILLS*
• STRESS COPING MECHANISMS*
• MENTAL CLARITY*
• IMMUNE SYSTEM FUNCTIONS*

BEHAVIOR AND SOCIAL SKILLS SUPPORT*:
• Dimethylglycine (DMG) has been reported to modify and improve behavior, eye contact, social interaction, verbal skills, mental alertness, brain function and may help reduce lethargy.* It is a precursor to many amino acids and neurotransmitters that aid in brain and nerve function.*
• Betaine (trimethylglycine) helps support balanced behavior, increased social interaction, circulation, normalized amino acid metabolism and liver protection from fat deposits.*
• Vitamin B6 supplementation result can result in a positive impact on behavior, better eye contact, less involuntary physical action and more interest in participation.*
• Folic acid helps in the metabolism of the amino acids used by the brain.*
• Vitamin B12 supports proper sleep patterns and production of the neurotransmitter acetylcholine, which assists in memory and learning.*

STRESS MANAGEMENT AND MENTAL CLARITY:
• Magnesium is a mineral that supports proper cognitive function and is essential for normal brain and nervous system functions.*

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leaves many of us in a quandary. How does one justify the use of a medical practice that in the opinion of most scientists should not work? As a result we are particularly attentive to scientific research that supports the use of this type of medicine.

It has been 2 decades since David Reilly’s *Lancet* articles, which showed homeopathic preparations of airborne allergens had significant impact on allergy symptoms, which prompted the editors of the *Lancet* to write “either there is something amiss with the clinical trial as conventionally conducted, or the effects of homoeopathic immunotherapy differ from those of placebo … carefully done work of this sort should not be denied the attention of *Lancet* readers.”1,2

Homeopathy was incorporated into Brazil’s Public Health Service in 2006. Petropolis was one of the first cities in Brazil to actively implement homeopathy. Petropolis was also the home of Roberto Costa and the Roberto Costa Institute.

The homeopathic medicines used in this study are somewhat unique. Roberto Costa, a homeopathic physician from Petropolis, developed a method of preparing nosodes using living organisms and reported they produced dramatic results compared to standard nosodes that are prepared from dead organisms.3 Costa’s reported results prompted an in vitro study published in 2013, which demonstrated that living nosodes prepared from influenza A virus had measurable effects—in particular stimulating macrophage cells and inducing an increase in tumor necrosis factor-alpha.4 These results motivated the present clinical trial to be conducted in the Brazilian Public Health System. These living nosodes are designated as “RC nosodes” after Roberto Costa.

These results seem too good. While almost a third of the children in the placebo group had 3 or more episodes of flu per year, use of either one of the homeopathic preparations tested in this study reduced episodes dramatically to just 1 episode in almost 300 children.

The timing of the study is another detail that makes the results seem implausible. This study was conducted during a year when Brazil was in the midst of the worldwide H1N1 flu pandemic. The pandemic reached Brazil between 2009 and 2010, but did so unevenly. The positive outcomes reported in this study occurred during a time when increased infection rates should have been expected.

We are thus obliged to look hard for potential errors in methodology that might account for misleading data.

Two states (out of a total of 23) were responsible for 73% of all influenza cases reported in Brazil that year.5 Could the children who received placebo have lived in an area of higher infection rates than those receiving the homeopathic medicines? The authors state that the treatment groups were randomized so that geographic location would not confound the data.

Siquerira et al are not just proposing homeopathic prophylaxis lowered risk of infection, but that it prevented 99% of the expected cases. In contrast, the CDC reports that this year’s flu vaccine (2016) has been “highly effective” at a 59% reduction.

The most obvious weakness in this study was that there was no actual laboratory examination of ill patients to confirm influenza infection. It would be more accurate to say that the children had something similar to an upper respiratory infection (URI) or influenza-like illness (ILI). It would be presumptive to state that these children actually had legitimate influenza infections based only on their questionnaires.

This lack of laboratory confirmation is shared by many complementary and alternative medicine trials and has been listed as a prime methodological consideration for investigating homeopathic treatment of influenza. Unless laboratory testing is employed to confirm the nature of a reported illness, the term ILI should have been used instead of influenza in discussing findings.
According to Paul Herscu, ND, DHANP, MPH, of the New England School of Homeopathy, studies are easily discredited when they claim to be about influenza but rely only on symptoms for diagnosis. This kind of criticism may sink a paper’s credibility. Whichever terms are ultimately chosen, the reader is nevertheless left with the fact that the treatment groups experienced far fewer episodes of apparent illness.

Another weakness in this Brazilian study is that it was dependent on, and may be weakened by, recall bias for the inclusion criterion, as well as recall bias during the actual trial. This is important since the actual time period during which the trial was conducted coincided with the 2009 H1N1 epidemic, a time when there would have been increased surveillance and increased reported incidence, not less.

Another factor that possibly affected recall bias is the Hawthorne Effect. The Hawthorne Effect is the positive change in the performance of a group taking part in an experiment or study due to their perception of being singled out for special consideration. Given the young age of the study participants, we might assume they would be far less sensitive to this effect, but perhaps their family or care providers who reported on symptoms of illness were influenced. Even so, this study was well blinded: Neither children, family, teachers, doctors, nor pharmacists knew whether the participant was singled out to receive active homeopathic medication or placebo medication.

Rates of actual influenza and illnesses are incredibly heterogeneous in Brazil, with a great deal of moveable pieces and fluctuating demographic changes to illnesses, making a trial difficult to understand, which is why we hope for laboratory confirmation.

In another paper describing the 2009 Brazilian flu epidemic, Oliveira et al reported, “There were 2,651 (45.6% of 5,817 acute febrile illness patients) ILI cases with a mean annual incidence of 60 cases/1,000 population (95% CI 58-62). Risk of ILI was highest among 5–9 year olds with an annual incidence of 105 cases/1,000 population in 2009.”

Science, good or bad, rarely stands in the way of public belief, and we will likely see this paper being used as justification for homeopathic influenza prophylaxis treatments this coming winter.

In Siquerira’s homeopathy study, 46 of the 151 children who had received placebo developed 3 or more flu or acute respiratory infection episodes. If this were only 1 episode per child, the incidence would equal 305 cases per 1,000. This would still be nearly 3 times the highest rate, or 7 times the average rate of illness that Oliveira et al report. These numbers are so far above the general infection rates reported elsewhere that it raises questions and cause for concern.

In contrast, the CDC reports that this year’s flu vaccine (2016) has been “highly effective” at a 59% reduction.

Even applying Oliveira’s reported incidence rate of 105 cases out of 1,000 to the 294 children who received homeopathic treatment and completed the study, we would extrapolate that 31 should have fallen ill during the year. Again, reporting that only 1 child became ill seems incredible.

Siqueira et al do not report vaccination rates among their study participants and whether rates varied among treatment versus placebo groups. More than 89 millions doses of H1N1 vaccine were administered during the course of this study in Brazil. While one assumes that randomization created subgroups that were equally vaccinated, this missing information raises the possibility that lower vaccination rates among
the placebo group might be linked with higher incidence of infectious episodes.

The nature of the questionnaire Siqueira et al used to measure the effectiveness of the homeopathic interventions allowed for tracking frequency of perceived illness but not severity. It is typical to report these 2 measures together as a way to judge the effectiveness of an intervention. One way to do so is by reporting the number of severe acute respiratory infections (SARIs), as in the paper cited below. Missing this more quantifiable measure of illness leaves the door open for conjecture; for example, is it possible that those individuals treated with homeopathic medicine had fewer episodes but that each episode was more severe or life threatening? Another possibility is that the placebo group had more frequent illnesses but of less severity.11 The authors did report that the children receiving the homeopathic preparation were more likely to have mild flulike symptoms in the month following initial treatment, while those children receiving placebo were more likely to have flulike symptoms about 3 months after treatment and then repeatedly. One might argue that this was a “homeopathic proving” or an immunological response to the treatments. If the latter, it would be curious to have looked for changes in viral antibody titers pre- and post-interventions.

Future trials like this would benefit from tracking symptoms and illness severity—and using lab testing to confirm flu infection.

Science, good or bad, rarely stands in the way of public belief, and we will likely see this paper being used as justification for homeopathic influenza prophylaxis treatments this coming winter. Given the low side effect risk of these medicines, there is little reason to dissuade people from engaging in such practices. Whether these Roberto Costa (RC) nosodes become available in North America is another question. Perhaps as we gain clinical experience using these products, my initial doubts about these incredible results will change.

REFERENCES