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Natural Childbirth and Breastfeeding as Preventive Measures of Immune-Microbiome Dysbiosis and Misregulated Inflammation

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Abstract

Much of the prior century was spent applying the latest emerging technologies toward managing pregnancy, childbirth, and infant development. The idea was that each change was significantly improving the health of our children across their lifetime. But it is now clear that with several of the adopted practices, there have been unintended consequences. We have run the risk of losing certain distinct advantages that were inherently embedded in ancient cultures and practices. Among these were the microbial-rich experiences of natural childbirth, breastfeeding, and agrarian living. These practices permitted children to acquire a complete microbiome thereby facilitating immune development and appropriate later-life immune responses. Perceived technology-associated benefits such as scheduled Caesarian births, urban sanitized living, and earlier and ever increasing vaccine burdens have helped to reduce the burden of some childhood illnesses. But recent studies suggest that they have also produced serious, unanticipated consequences for today's children: an increased likelihood for human-microbiome incompleteness, lifelong immune dysfunction, and inflammation-promoted chronic disease. This review will examine recent evidence suggesting that a more effective blending of ancient practices and remedies with modern technology and medical knowledge could help to restore the human-microbiome super organism to its historic status, improve pediatric immune homeostasis and reduce risk of later-life chronic diseases.

Keywords: Vaginal delivery; Caesarian delivery; Immune development; Microbiome; Chronic diseases; Maternal microbiota; Hygiene hypothesis; Developmental basis of adult disease; Inflammation; Epigenetic programming

Introduction

Preventive strategies have been employed for centuries across civilizations to reduce the risk of both general maladies and specific diseases. Examples include: 1) Captain Cook's use of various antiscorbutic agents to prevent scurvy among his crew [1], 2) the suggestion to clean the house more frequently, remove dead rats, and visit the countryside to protect against the plague in 19th century China [2] and, 3) public education during the 1917 Spanish flu epidemic concerning the covering of coughs and sneezes and awareness of apparently-healthy carriers of the virus [3]. Knowledge of these connections between specific actions and reduced risk of disease was developed after years, decades, or even centuries of significant prior human loss from the same diseases.

Two of the longest-standing and probably most effective preventive measures against childhood and adult disease are natural childbirth (NC) [used here to mean vaginal delivery (VD) with as little use of drugs/antibiotics as is possible] and breastfeeding of the infant. These two practices have always been prominent throughout human history and were most often the default strategy; however, we have witnessed a recent cycle in which technology-supported alternatives have, at least temporarily, replaced natural childbirth and breastfeeding as the most prevalent strategies. Caesarian delivery (CD), including both medically necessary and elective procedures, and formula feeding of infants saw dramatic increases in prevalence during the 20th century. These were seen as suitable alternatives to the natural processes where the immediate gain for the mother and child was far more obvious to the medical and public health communities than were the longer-term health risks to the offspring. Technological achievements provided the options for selection of birth and feeding processes. Ironically, the relatively rapid and extensive shift toward these alternatives between the 1930s and 1970s has been reversed in many countries, and there is now a major public health advocacy effort to return to the more historic birth and infant feeding practices. As discussed by Wolf [4], there is an irony that early in the 20th century public health officials were advocating increased breastfeeding by mothers and early in the 21st century the same exact message has been repeated albeit with a different mix of reasons [4]. In the case of the 20th century call for increased breastfeeding, the primary health concerns were for acute illnesses such as diarrheal diseases, pneumonia, and necrotizing colitis [4]. But for the more recent call, the preventative focus is larger and includes the prevention of noncommunicable chronic diseases (NCDs) [5].

This review considers: 1) shifting historic views regarding the value of natural childbirth and breastfeeding as preventive measures, and 2) an emerging paradigm in which natural childbirth (NC) and prolonged infant breastfeeding combine to reduce the risk of inflammation-driven chronic diseases via immune-microbiome co-maturation as well as other possible developmentally-programmed routes. Additionally, NC and breastfeeding are discussed under the broader human ecological framework of a developmental model in which effective human-microbe super organism formation between the child's mammalian component and symbiotic microbes that form the child's microbiome, termed the "Completed Self" [6]. Timely, complete and individualized formation of this symbiotic human mammalian-microbial organism or "Completed Self" has been suggested as perhaps the single most important biological sign connected to a lifetime health trajectory of the individual [6].

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Finally, the cycle through which natural childbirth and breastfeeding have either been favored and promoted by science-driven health policies or fallen into comparative disfavor (*vs.* CD and formula feeding) is discussed relative to health risk-benefit assessment. The lesson of experiencing two separate public health campaigns to increase the prevalence of prolonged breastfeeding that were divided by 50 years of a contradictory public health messages should provide a useful cautionary note regarding future health safety assessment and policy.

Vaginal *vs.* Caesarean Delivery: Changing Trends and Potential Implications

Childbirth itself, regardless of the delivery mode, is not risk-free and as a result, there are risk-benefit considerations to weigh for both the mother and the child [7]. Among the more recent considerations for the child has been recognition of longer-term immune implications connected with birth deliver mode [8]. VD has been shown to prime the newborn with bacterial communities that are directly related to those of the mother's vaginal microbiota [9]. These maternal-derived microbes of the newborn, in turn, become establish in mucosal tissues and play an important role in maturation of the innate immune system and the acquisition of effective immune homeostasis (i.e., balanced responses in tissues) [10]. At issue are the health implications arising from the developmental immune processes connected to mode of delivery.

CD has proven to be a useful delivery mode in cases of medical necessity where the imminent health of the mother or child would be unduly jeopardized by VD. Examples of medical or obstetrical complications that can trigger CD can include fetal stress (e.g., abnormal heart or breathing rate), maternal infections and health problems (e.g., genital herpes, HIV, preeclampsia), labor problems (e.g., breech position), and placental or umbilical cord challenges (e.g., umbilical cord prolapse) [11]. But the significant increase in CDs and need to better distinguish among levels of medical necessity are leading to audit-type processes to improve risk-benefit vetting of the procedure [11-13]. Prophylactic antibiotics are often administered around the time of the operation and, while the risk of infections for the mother appears to be lowered by antibiotic administration, the range of implications for the child remains uncertain [14].

Elective CDs, those for non-medical reasons, have increased significantly in recent years. For example, a Swedish registry study for birth during the years 1997-2006 found a three-fold increase in elective full-term CDs during this interval [15]. Although the long-term effects of VD *vs.* CD remain to be fully established, the reported association of CD with a higher prevalence of many pediatric immune dysfunction-driven, persistent, chronic diseases [16-18] as well as the known pattern of comorbid interlinkages among immune-based chronic diseases [19-21] suggests that a difference in later-life chronic disease burden associated with CD may be likely. In a recent review, Hyde and Modi [22] included metabolic syndrome-associated disorders, immune-related diseases, gastrointestinal diseases, cancer, and neurodevelopmental conditions among the categories of elevated health risks that have been associated with CD.

CD is not a modern-day invention but rather dates back to ancient times [23]. But there are important distinctions between its ancient use and more recent applications. Centuries ago, the procedure was done to save the child when the mother would not survive. Roman law (*Lex Cesarea*) decreed that Caesarian delivery would be attempted on all women with child who were dead or dying [24]. This pattern of intended use of CD held throughout much of history. It was applied only when the mother's death was certain.

The first purported CD where the mother survived was described as occurring in 1500 but the account itself was not recorded until the 1580s and is in some dispute [25]. The first reported survival of the mother following CD in England was recorded in 1793 [26]. It remained a relative rare procedure as described for Ireland in the early 19th century [26]. Even the advent of the antiseptic era introduced by Lister did not improve the prognosis for the mother as the surgical procedure itself left much to be desired until the late 19th century [25]. The maternal mortality rate was reported as 84% in England in 1876. Surgical advances paired with the discovery of antibiotics by Fleming during the 20th century greatly reduced the risk of the procedure.

O'Sullivan [26] identified the 1950s as the era where a major change occurred in the use of CD during which operative obstetrics increased significantly and "active intervention" became a prevailing motto. Some British medical specialists worried that the birth canal had been relegated to a secondary makeshift status [26].

The rate of CD has increased at an alarming rate in recent decades. For example, based on data from National Health Service trusts in England, the rate doubled between the years 1990 and 2008 [27]. CDs now constitute between approximately one-quarter to nearly one-half of all births depending upon the country. For example, the prevalence of CD has risen to estimates of 24% in England [27], 33% in the US [28] and 40% in some regions of India [29]. An estimate for Brazil is between 32-48% depending upon the country of the mother's birth [30]. Finally, a study sponsored by the World Health Organization estimated that in China, almost one-half (46%) of all women were having CDs [31].

In fact the dramatic increase in rates has led some countries to advocate for target goals aimed at reducing rates [32]. But as Burrow [32] points out, a "technological imperative" has seeped into decision-making considerations adding pressure to the physician and patient and potentially reducing the mother's underlying choice. Burrow [32] argues that women need access to enough information to make relevant decisions free of technological pressure.

Additionally, Bonifacio et al. [33] studied the outcomes among 1650 children (n=495 delivered by Caesarian section) born to a parent with type 1 diabetes. Children from Caesarian delivery who also carried an immune-associated genetic risk factor had a greater than two fold elevated risk for developing type 1 diabetes over those delivered by conventional VD. Ironically, Niebyl et al. [24] suggest that the recent increase in prevalence of inflammatory-driven diseases and conditions such as obesity and diabetes mellitus may have contributed to the increased prevalence of CD. If correct, this would represent quite a vicious cycle in which the present existence of chronic diseases inhibits a preventative measure that could reduce the risk of inflammation-driven chronic diseases in the subsequent generation.

Breastfeeding vs. Formula Feeding of the Infant

The history of using wet nurses, the feeding bottle, and formula feeding was recently reviewed by Stevens et al. [34]. Concern over the need to provide the newborn with an adequate and appropriate food supply has been an ancient concern. Osborn [35] describes the use of wet nurses in ancient Greece and Rome primarily as a needed alternative. It evolved to the status of a potential choice by the Renaissance period, and this persisted well into the 19th century [36]. While use of alternatives to breast milk dates to ancient times [34], including cow's milk [37], the development of what were considered safe formulas for feeding are largely a 20th century phenomena [38].

Several organizations have supported the return to exclusive

and prolonged breastfeeding as a primary, postnatal, nutritive and health-supporting practice for the infant where benefits extend across a lifetime. In 1989, The World Health Organization and UNICEF coauthored a report advocating support for mothers to aid an increase in breastfeeding [39]. In 2009, the American Dietetic Association published a position paper advocating prolonged breastfeeding [40]. In 2011, the Office of the US Surgeon General issued a health report advocating exclusive and prolonged breastfeeding for improved immune protection and reduced risk of obesity and other chronic conditions [41]. The American Academy of Pediatrics recently reaffirmed that infants should be breastfed exclusively for a minimum of six months and that breastfeeding be continued until at least one year of age as complementary foods are introduced [42].

As discussed by Wright and Schanler [43], breastfeeding in the US hit an apex of approximately 70% of infants about 1915 falling to a low of 22% in 1972. In recent years, the percentage has begun to increase again with a rate of 76.4% recently reported for initiation of breastfeeding [44]. However, even with the increasing trend, there is concern that the duration of breastfeeding is less than optimal. In a recent CDC summary report, fewer than half of all infants in the U.S. were still being breastfed at six months of age and that percentage drops to below one-quarter by 12 months of age [45].

Completion of the Human-Microbial Superorganism during Childhood

One of the important findings in the recent research on the human microbiome is that the microbial cells in human tissues outnumbered our mammalian cells by at least a factor of ten [46]. For this reason, seeding and nourishment of the microbial partners (the microbiota) of children represent key developmental processes. These microbes are symbiotic with humans and are needed to form what has been termed the human-microbiome super organism. Mulder et al. [47] found that a narrow critical window exists in early life during which the microbial seeding of the infant largely determines the progression of the microbiome and immune maturation into adulthood. For this reason, those developmental events that largely define the human-microbial super organism take on an added significance in developmental programming of later life health.

In fact, Dietert and Dietert [6] recently posited that if effective microbiome formation is inhibited in the infant, we essentially exist as an ecologically-incomplete organism. The event of infant self completion, in which the human mammalian component is joined symbiotically with an individually-tailored microbiota, is probably the single most important sign that will distinguish health from disease in that individual. An efficiently- and effectively-formed human-microbe superorganism is what Dietert and Dietert termed, "The Completed Self" [6]. This concept is compatible with the proposal of Erberl [48] that a major purpose of the immune system is the homeostasis involved in managing the microbiome of the superorganism. Proper seeding and completion of self during early infancy has long term ramifications. For example, some evidence suggests that early life gut microbiota tailored to the infant's system, such as *Bifidobacterium longum* subsp. *infantis*, can depress proinflammatory cytokine (e.g., TNF-α) levels and dampen down the inflammatory response at crucial windows of mucosal tissue development [49]. Improperly controlled inflammation in early life appears to promote later-life health problems. One of the suggested solutions for mucosal immune-microbiome dysbiosis and the associated elevated risk of both acute infections as well as chronic diseases has been fecal microbial transplantation [50,51]. However, to date, this remains a comparatively infrequent treatment [52]. Of note is the observation of Bengmark [53] that pharmacological drug efforts to overcome an incomplete microbiome have been largely unsuccessful, and that food practices of the past supporting early establishment of the proper microbiome is the most effective route to a healthier life [53].

The Infant Microbiome in Immune Development and Disease

Neonatal maturation of the immune system is greatly influenced by the microbiota in mucosal tissues with both innate and adaptive immunity affected via the interactions in the symbiont (an organism in a symbiotic relationship) [54-56]. In a recent review of the gut microbiome and immune disorders, Hwang et al. [57] and Kelly and Mulder [58] discuss what could be termed an extended hygiene hypothesis.

At birth and for weeks to months thereafter, the newborn is seeded with microbes from the mother as well as through other environmental sources. Specific species of microbes take up residence in the gut, other mucosal tissues and the skin and help to drive four critical health-related activities: 1) crafting postnatal development of the mucosal immune system, 2) supporting immune-tissue homeostasis, 3) contributing to infant and later-life dietary metabolism, 4) helping control the access of pathogenic microbes to these environmentally-accessible sites. This balance appears to be crucial in regulating subsequent immune responses and avoiding inflammation-driven disease. Recently, Dielh et al. [59] demonstrated in a mouse model that steady-state commensal bacteria help to compartmentalize immune stimulation by restricting the transport of commensal and pathogenic bacteria in the gut to the mesenteric lymph nodes (sites of immune response stimulation). This homeostatic regulation limits the likelihood of misregulated inflammation, which could promote chronic diseases such as inflammatory bowel disease (IBD). Children with IBD have been reported to have an altered gut microbiome compared with those without the disease, although it is not known for certain if the altered microbiome is causative of the disease [60]. The association of dysbiosis, including abnormal microbiota and, in particular, a reduced complexity of the gut microbial ecosystem, appears to be a hallmark of IBD [61]. Gut microbiota are not the only microbial factor. Kong et al. [62] found that perturbations in skin microbiota are important in atopic dermatitis flares. As seen with gut microbiota, a reduced diversity of skin microbes has been found in infants with atopic dermatitis as compared to healthy infants [63].

Table 1 provides examples of the reduced health risks reported to be associated with natural childbirth [VD and prolonged breastfeeding (four-six months exclusively then breastfeeding with complementary feeding)]. Other disease associations of symbiotic microbial dysbiosis have been suggested. However, it should be noted that not all studies in the literature show significant associations. Two possible explanations for this are that some subpopulations may benefit more than others from these measures in protection against diseases such as asthma (Table 1), and earlier life problematic environmental exposures (e.g., in utero conditions) could blunt the effectiveness of later postnatal measures.

Knip and Simell [64] argue that onset of type 1 diabetes is preceded by the appearance of proinflammatory metabolic serum profiles, and that this inappropriate inflammation may be connected with the gut microbial dysbiosis seen in type 1 diabetes patients. A similar relationship has been reported for microbial dysbiosis and risk of atopy/allergic disease. Again, the presumption is that inappropriate

Vaginal *vs.* Caesarian Delivery (CD)	Disease/Condition Category	Reported Reduced Risk (Diseases/Conditions)	Reference(s)**
	Allergic	Asthma	[16,95]
	Allergic	Atopy	[95]
	Autoimmune	Celiac disease (elective CD only)	[96]
	Autoimmune	Inflammatory bowel disease	[97]
	Autoimmune	Multiple sclerosis	[98]
	Autoimmune	Type 1 diabetes	[99,100]
	Cancer	Childhood myeloid leukaemia	[101]
	Metabolic/Inflammatory	Obesity	[102,103]
Prolonged Breastfeeding* *vs.* Short Duration Only and/or Formula Feeding**			
	Allergic/Infectious	Otitis media	[104]
	Autoimmune	Type1 diabetes	[105]
	Infectious	Necrotizing entercolitis	[106]
	Infectious	Respiratory infections	[107,108]
	Allergic/Inflammatory	Asthma	[109,110]
	Inflammatory	Sudden infant death syndrome	[111]
	Metabolic/Inflammatory	Obesity	[112]
	Metabolic/Inflammatory	Type 2 diabetes	[113]
	Neurological	Cognitive impairment	[114]

*Note that not all studies report significant, reduced disease associations for these two preventive measures.This may be due in part to subpopulation and prior exposure effects. For example, Braback et al. [115] found that confounding familial factors affected the associations of birth delivery mode and risk of asthma. Likewise, Hancox et al. [116] pointed out that the gene-environment interactions are probably important among the specific birth cohorts examined for breastfeeding and asthma.

**The references shown are not intended to be an exhaustive list. Instead they are representative of reported health risk associations. An additional discussion of the short- and long- term implications of CD can be found in Hyde and Modi [22] and Hyde et al. [117].

***For this comparison, prolonged breastfeeding refers to at least 4-6 months of exclusive breastfeeding followed by additional breastfeeding with possible complementary foods. In these studies, exclusive breastfeeding was compared vs. formula feeding from birth or a shorter duration of breastfeeding usually followed by formula feeding then solid foods.

Table 1: Examples of Reported Reduced Health Risks Associated with Natural Childbirth and Breastfeeding*.

inflammation is a pivotal factor promoting elevated risk of disease [65]. Iebba et al. [66] suggested that Lactobacillus and Bifidobacterium species may be generally be protective against atopic diseases, while Clostridia, Enterobacteriaceae, and staphylococci may drive Th-2 mediated diseases.

Infant Microbiome and Control of Inflammation

There appears to be a series of life stage-related shifts in microbiota that occur during a healthy life trajectory that may be important in effective postnatal immune maturation and homeostasis. Avershina et al. [67] described a networked, age-related progression of different *Bifidobacterium* species in primarily vaginally-born, breast-fed infants that occurred across the first two years of life. For example *B. adolescentis* was generally only found in younger infants and was lacking both at 1-2 years of age and in the adult. The researchers attributed the progression of species changes to healthy maturation of the gut and the mucosal immune system as well as shifts in nutritional requirements. Pozo-Rubio [68] reported that the proportion of different *Bifidobacterium* species could affect the balance of cytokines produced among immune cells. For example, a mixture rich in *B. infantis* and *B. adolescentis* tended to stimulate less interferon-gamma production than a mixture rich in *B. breve*. The composition, numbers and activity of the specific microbial species appear to be factor in control of immune-driven inflammation.

Breastfeeding and Microbiome Support

Human breast milk provides a source of both specialized nutrients as well as specific bacteria that can colonize the infant's gut. Figure 1 illustrates the combination of effects resulting from natural childbirth and breastfeeding on the infant's microbiome and postnatal immune status. Sela and Mills [69] found an exquisite interplay between milk oligosaccharides in human milk and *Bifidobacterium longum* subsp. *infantis,* which are tailored to be able to digest and utilize these specific oligosacchariades. In contrast, adult-associated bifidobacteria lack that capacity. Some of the same specific glycans found in human breast milk are important in enabling the innate immune cells to respond to pathogens [70]. Sela and Mills [69] point out that while nutraceutical mimics of human milk oligosaccharides have been developed, two important qualities remain uncertain: 1) whether these mimics can retain the same immune and pathogen deflection capacity as that of human milk, and 2) whether they fully support the infant-type version of bifidobacteria vs. more general populations and pathogens.

In an necrotozing enterocolitis animal model, there is the suggestion that a combination of probiotic bacteria and breast milk synergize to produce an elevation in the percentage of Fox3p(+) regulatory cells (Tregs) [71]. In contrast, administration of probiotic bacteria alone (e.g., in formula fed rats) failed to alter the Treg population of the diseased ilium [71]. This suggests that a combination of infant microbial seeding and breast milk may be particularly useful for effective control of inflammation.

Supportive results were found among infants fed breast milk exclusively. Kainonen et al. [72] reported that infants fed breast milk vs. formula had an anti-inflammatory cytokine millue throughout

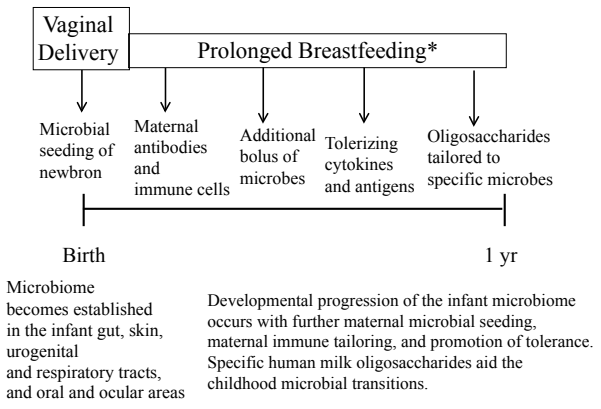

Figure 1: Combined Effects of Natural Birth and Breastfeeding on Immune-Microbiome Development. The figure illustrates the complementary contribution of immune factors, microbes, antigens, and nutrients tailored to support those microbes that the newborn-infant obtains from natural childbirth (VD with minimal medical/drug intervention) followed by prolonged breastfeeding (*defined here as at least 4-6 months of exclusive breastfeeding followed by breastfeeding possible combined with complementary foods). Individually, natural childbirth and breastfeeding each provide benefits for the infant. However, recent research suggests that the combination of these two long-standing preventive measures provides the necessary components for both human superorganism self-completion and effective commensal-supported immune maturation and homeostasis. The latter is needed to minimize immune dysfunction, misregulated inflammation, and an elevated risk of later-life chronic disease.

infancy. These authors concluded that this was more likely to promote tolerance and reduce the likelihood of hyperresponsiveness and allergic disease. Using a human prospective birth cohort of 291 healthy term neonates, Belderbos et al. [73] reported that breastfeeding significantly modulated innate immune function (e.g., elevated TLR-7 mediated IL-10 cytokine production) compared with formula feeding. Breast milk is also rich in the immunomodulatory, TNF-related, apoptosis-inducing ligand (TRAIL), which is absent in formula [74,75].

Other Routes and Considerations for Developmentally-Programmed Health Outcomes

Seeding and nurturing the child's microbiome for key immune interactions are not the only considerations for developmentally programmed immune status and health risks. It appears that microbe-facilitated immune maturation can be nullified by problematic exposure during critical windows of development to other environmental factors. For example, Hoppin et al. [76] reported from the U.S. National Agricultural Health Study that direct exposure to pesticides appeared to nullify the beneficial aspects for women of growing up on a farm relative to risk of atopic asthma. Mai et al. [77] also found that a largely fast food diet could undermine the beneficial aspects of breastfeeding relative to risk of asthma.

In addition to the infant microbiome-immune development paradigm discussed in this paper, other models have been suggested to explain, at least in part, immune alterations and long-term health outcomes associated with the critical window of childbirth (the intrapartum period). In a recent paper, Dahlen et al. [78] raised the issue of whether the lack of exposure to diverse microorganismsin early childhood (known as the "hygiene hypothesis") could fully explain the array of adverse health outcomes associated with CD such as those illustrated here in Table 1.

In a model known as epigenetic impact of childbirth (EPIIC), these investigators argue that labor is a critical life event and labor interventions such as CD could alter perinatal stress-driven physiology and epigenetic imprinting that can program for later-life immune and health problems [78]. Dahlen et al. [78] suggest that childbirth, rather than being viewed as a supportive event of prenatal development, is itself a significant formative event capable of physiologically reprogramming the fetal epigenome. As with other example of epigenetic programming, there is the potential for transgenerational health implications. There are several lines of supporting information: 1) evidence suggests that macrophages and inflammatory processes play key roles in directing full and pre-term labor [79], and there are feedback effects on the immune and neurological systems arising from vaginal birth [80], 2) early life stress can produce epigenetic programming affecting risk of immune dysfunction-driven chronic disease [81,82] 3) birth delivery mode (VD vs. CD) has been reported to affect DNA methylation patterns of leukocytes [83].

Complementary Preventive Measures

A final note is that natural childbirth (VD)(with no drugs and antibiotic administrations when possible) and breastfeeding are not merely two separate useful events in a child's life. Instead, they are remarkably complementary. Beyond the relatedness of events depicted in Figure 1 with VD and breastfeeding, the other conditions surrounding a natural birth featuring more maternal-infant contact and a reduced drug burden can support human-microbial super organism completion and the immune maturation trajectory.

The level and nature of certain medical interventions surrounding birth is thought to potentially impact the infant's initial and subsequent microbiota [84]. For example, exposure to antibiotics and some other drugs have been reported to alter both microbiome formation and/or immune maturation [85-87]. In contrast, there are suggestions that certain forms of supportive contact surrounding birth can aid infant feeding even in the premature infant. For example, maternal-infant skin-to-skin contact immediately after birth of full term infants can aid health-promoting mother-infant behavioral bonding [88] as well as facilitating both breastfeeding [89,90] and cardio-respiratory stability [91] . The more prolonged skin-skin contact used for premature infants (known as Kangaroo care) has been reported to reduce the risk of infections [92] and support breastfeeding [93]. Additionally, with premature births and feeding concerns, specific music therapy, such as recorded music of lullabies that the parents prefer, has been reported to: 1) entrain heart and breathing rates, and 2) increase both sucking behavior and caloric intake [94]. The two preventive processes, natural childbirth and breastfeeding, can be viewed as a useful continuum for effective developmental programming of immune-microbiome homeostasis.

Conclusions

With technology-driven health advancement has come the realization that at least some of the changes in public health have unintended and largely unrecognized health consequences associated with them. Two of these cases are discussed in this review: Caesarian delivery and formula feeding. More immediate benefits were obvious and sufficiently significant during the 20th century such that widespread medical and social changes were adopted. But it has become apparent that long-term health risks were underestimated due to a critical gap in

the knowledge base of fundamental biology and the human-microbial ecosystem.

Natural childbirth, when medically possible and prolonged breastfeeding are among the easiest preventive measures against later life disease. We now realize that the protection is not restricted to infant infection and neonatal mortality but also includes a reduced risk of multiple chronic diseases across a lifetime. A pivotal factor in this protection appears to be self-completion in which the optimal human-microbial symbiont is formed early-on in each infant and is supported, in large part, via the components of human milk. The maturing immune system recognizes and manages the mammalian-microbial completed self and following this process of completion, there is a reduced likelihood of misregulated inflammation and its associated diseases. Other factors may be important as well as has been hypothesized with the EPIIC model of childbirth epigenetic programming. Mode of birth itself could exert a physiological reprogramming of the fetal epigenome affecting both immune function and risk of later life disease.

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