HHS Public Access

Author manuscript

Curr Opin Microbiol. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Curr Opin Microbiol. 2018 February ; 41: 8–14. doi:10.1016/j.mib.2017.10.023.

Bacterial Microbiota of the Nasal Passages Across the Span of Human Life

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Abstract

The human nasal passages host major human pathogens. Recent research suggests that the microbial communities inhabiting the epithelial surfaces of the nasal passages are a key factor in maintaining a healthy microenvironment by affecting both resistance to pathogens and immunological responses. The nasal bacterial microbiota shows distinct changes over the span of human life and disruption by environmental factors might be associated with both short- and long-term health consequences, such as susceptibility to viral and bacterial infections and disturbances of the immunological balance. Because infants and older adults experience a high burden of morbidity and mortality from respiratory tract infections, we review recent data on the bacterial nasal microbiota composition in health and acute respiratory infection in these age groups.

Introduction

The nasal passages are an important habitat for clinically relevant pathobionts (commensal bacteria that can cause disease in healthy hosts), e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, and are an important site of viral infections [1,2]. Morbidity and mortality from these pathogens are greatest in children and older adults. There is increasing evidence that commensal bacteria have a role in both shaping the communities inhabiting these surfaces, by impacting pathobiont behavior or colonization [1,3–7], and in modulating disease severity during respiratory viral infection by influencing the host immune response [8]. This review focuses on current research describing the bacterial microbiota of the nasal passages in children and older adults in health and acute infectious diseases, which builds upon a foundation of pioneering work [1,2,9]. The human nasal passages extend from the opening of the nose (nostrils or anterior

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nares) posteriorly to include the nasopharynx (top of the back of the throat) [1] and there has been a rapid expansion of literature describing the composition of bacterial microbiota of these epithelial surfaces. However, comparison across studies is hampered by the use of different variable regions of the 16S rRNA gene to characterize the bacterial microbiota (Table 1), and by the known and unknown biases introduced by differences in sampling site, sample handling, DNA extraction, library generation and sequencing platform. In spite of this, common themes are emerging from research across the globe, albeit most of it concentrated in developed nations. Below, we discuss these themes and summarize key gaps in knowledge and areas for future research.

Birth to Two Years: bacterial microbiota development and associations with route of delivery and feeding

Multiple studies in developed countries, and the few in developing countries, find that the bacterial microbiota of the nasal passages of infants are characterized by high relative abundances of the genera (family, phylum) *Moraxella* (*Moraxellaceae*, Proteobacteria), *Streptococcus* (*Streptococcaceae*, Firmicutes), *Haemophilus* (*Pasteurellaceae*, Proteobacteria), *Staphylococcus* (*Staphylococcaceae*, Firmicutes) and *Corynebacterium* (*Corynebacteriaceae*, Actinobacteria) with some studies also noting *Dolosigranulum* (*Carnobacteriaceae*, Firmicutes) and a few other genera (Table 1) [8,10–20]. Many of these studies identify four or more typical microbiota profiles each highly enriched for one or two of these genera.

Longitudinal studies reveal a developing microbial community that changes across the first year or more of life influenced by both host and environmental factors, including route of delivery and feeding, which may themselves be associated with each other (Table 1). A longitudinal study of western European infants, from birth to 6 months, reveals a common *Streptococcus*-enriched community 24-hours postnatal with a distinctly nasal microbiota (i.e., niche differentiation) starting by 1 week. However, there is a delay in the pace at which the NP microbiota develops in infants born via Caesarian section (CS) and a reduction in colonization by *Corynebacterium* and *Dolosigranulum* [16]. By contrast, a smaller study reports higher microbial community richness in CS-delivered infants [14]. In a U.S.-based study, *Propionibacterium, Lactobacillus*, *Streptococcus*, *Staphylococcus* and *Corynebacterium* are the most abundant genera detected from the nares (nostrils) on the day of delivery regardless of route, with the relative abundance of *Lactobacillus* and *Propionibacterium* decreasing and that of *Moraxella*, *Staphylococcus* and *Corynebacterium* increasing over the first six weeks [21]. Minor differences, if these exist, in bacterial microbiota composition at birth based on delivery route are transient and disappear by six weeks [21]. This observation led the authors to hypothesize that body site, rather than delivery route, drives postnatal bacterial community acquisition. Differences in the findings between these three studies highlight the need for further investigation into the impact of route of delivery on the bacterial microbiota of the nasal passages.

Research has also explored whether route of feeding influences early development of microbiota in the nasal passages. In breastfed infants from western Europe and western

Australia, members of the families/genera *Staphylococcaceae*/*Staphylococcus* and *Corynebacteriaceae*/*Corynebacterium* are enriched (i.e., have higher relative abundance) in the bacterial microbiota of the nasal passages at 6 to ~12 weeks of age compared to other taxa [12,13]. In a different European study, the nasopharyngeal (NP) bacterial microbiota of exclusively breastfed infants at six weeks of age is characterized by *Dolosigranulum*- and *Corynebacterium*-enriched profiles, whereas that of exclusively formula-fed infants shows an overrepresentation of a *Staphylococcus*-enriched profile [11]. Similar to route of delivery, differences between breast- and formula-fed infants are transient and disappear by six months of age [11]. It remains to be determined whether these transient differences affect the developing immune system in a way that impacts subsequent susceptibility to respiratory diseases and/or other long-term health consequences.

The pattern of early bacterial colonization over the first few months of life may play a role in the stability of the nasal bacterial microbiota [10]. In one study, early colonization with and higher relative abundance of *Moraxella* and *Corynebacterium*-plus-*Dolosigranulum* are associated with increased microbiota stability over the first two years of life [10]. Increasing age also correlated with an increase in the prevalence and relative abundance of *Moraxella* [10,13]. By contrast, high abundance of *Haemophilus* and *Streptococcus* correlated with less stable microbiota composition [10,13]. However, stability is not static with nasal microbiota showing seasonal variations in temperate climates [12,22], which might not extend to healthy children in climates with less seasonal variation [13].

Associations of infant nasal bacterial microbiota and respiratory tract infections

Infancy and early childhood are characterized by frequent acute respiratory tract infections (ARIs), mostly due to viruses, e.g., human rhinovirus (HRV) and respiratory syncytial virus (RSV). Recent cross-sectional and longitudinal studies have explored the hypotheses that the bacterial nasal microbiota composition is impacted by ARIs and/or impacts ARIs in terms of susceptibility to clinically apparent infection and severity of disease (Table 1) [8,13,17–20,23–29].

One area of active investigation is whether bacterial nasal microbiota might be associated with susceptibility to and/or severity of bronchiolitis, which accounts for 18% of infant hospitalizations in the U.S. and is a risk factor for subsequent development of asthma [30]. The 35th Multicenter Airway Research Collaboration (MARC-35) reports on a multicenter cohort study of 1005 infants under one year hospitalized with bronchiolitis, who are then being followed prospectively for development of asthma (Table 1). A cross-sectional comparison of a subset of 40 bronchiolitic infants to 110 age-matched healthy controls found that the percentage with bronchiolitis was lower in those with *Moraxella*-enriched and *Corynebacterium-Dolosigranulum*-enriched profiles and higher in those with a *Staphylococcus*-enriched profile [20]. In the full MARC-35 cohort of 1005 infants hospitalized with bronchiolitis, there were four NP microbiota profiles: either enriched for *Haemophilus, Moraxella*, *Streptococcus* or a mixed profile, and the rate of severe bronchiolitis (ICU admission) was highest in the *Haemophilus*-enriched profile group, even

after adjusting for confounders, and lowest in the *Moraxella*-enriched group [24]. MARC-35 researchers are also exploring whether these microbiota-severity associations correlate with host immune response (e.g., NP CCL5 [25] and serum LL-37 [26]). Inferences from this large cross-sectional analysis of infants hospitalized with bronchiolitis argue strongly for large longitudinal studies from birth to detect if bacterial microbiota profile is a risk for severe bronchiolitis.

A few studies have examined correlations between NP microbiota composition and infection with the common upper respiratory tract (URT) viruses, HRV and RSV. The variation in results, as described below, supports the need for more such studies. Analysis of the 760 MARC-35 hospitalized bronchiolitic infants infected with HRV and/or RSV found that NP microbiota profiles differed in infection due to RSV, HRV or coinfection. A high relative abundance of Firmicutes, and *Streptococcus*, and a low relative abundance of Proteobacteria, and *Haemophilus* and *Moraxella*, was found in RSV infection, while the opposite was found in HRV infection and somewhere in between in coinfection [28]. Another comparison of infant NP microbiota in HRV versus RSV ARI (~74% outpatient) found greater alpha diversity with HRV and increased relative abundance of *Staphylococcus* with RSV [29]. However, there were no differences in terms of relative abundance in the five numerically dominant genera (*Moraxella*, *Streptococcus, Corynebacterium*, *Haemophilus* and *Dolosigranulum*) in HRV versus RSV [29]. In a study on RSV comparing children under 2 years who were either hospitalized with RSV, outpatient with RSV or healthy (n=132 total), hospitalization due to RSV infection was positively correlated with *H. influenzae*- or *Streptococcus*-enriched NP microbiota profiles and negatively correlated with a *S. aureus*-enriched profile [8]. This same cross-sectional study observed differential expression of immunity genes in healthy children compared to 1) all those with RSV disease (IFN-related) and 2) those with RSV disease and either *H. influenzae*- or *Streptococcus*-enriched profiles. The authors postulate that nasal bacterial microbiota composition influences the host immune response to RSV infection, thereby modulating disease severity [8].

Preceding viral URT infection is a known risk for bacterial pneumonia. A *Haemophilus*-enriched NP profile has also been associated with pneumonia in a cross-sectional study comparing NP bacterial microbiota of children in Botswana under one year who were either healthy, had pneumonia or had symptoms of URT infection [18]. A *Streptococcus*-enriched profile, characterized by low levels of *Corynebacterium/Dolosigranulum*, and a *Staphylococcus*-enriched profile were associated with pneumonia, whereas *Streptococcus*- and *Moraxella*-enriched profiles were associated with URT symptoms [18].

Although the above cross-sectional studies (Table 1) suggest differences in nasal bacterial microbiota in relation to viral presence and infection severity, longitudinal sampling is necessary to determine whether such differences are the consequence of viral infection or whether certain microbiota profiles are associated with increased risk for infection and/or more severe disease. For example, a study sampling the same children at 2, 6 and 12 months found that profiles enriched in *Corynebacterium* plus *Alloiococcus* (which the authors note might be *Dolosigranulum*) and *Staphylococcus* are associated with a decreased risk of ARI, whereas *Moraxella-, Streptococcus-* and *Haemophilus*-enriched profiles are associated with an increased risk of ARI [13]. Similarly, a study of infants from 2 hours after birth to 12

months of age found early acquisition of *Moraxella*-enriched communities is associated with more ARIs in the first year of life, and prolonged maintenance of *Corynebacterium-Dolosigranulum*-enriched communities with fewer [17]. In this study, route of delivery, route of feeding, crowding and antibiotic exposure are described as independent drivers of this altered microbiota development. In another longitudinal study, early colonization with and higher relative abundance of *Moraxella* and *Corynebacterium*-plus-*Dolosigranulum* were associated with lower parent-reported frequency of ARIs [10]. By contrast, one longitudinal sampling of healthy infants over the first year of life detected no associations between nasal bacterial microbiota composition and the likelihood of subsequent HRV colonization/infection [27]. However, it did detect microbiota changes during and after symptomatic infection with a loss of alpha diversity and increased bacterial density during symptomatic HRV infection, compared to asymptomatic colonization, and lower alpha diversity at study end in the nasal bacterial microbiota of infants with more frequent symptomatic HRV. Also, following symptomatic HRV infection, there was higher relative abundance of *Moraxellaceae* and lower relative abundance of *Staphylococcaceae* compared to virus-free samples [27].

Viral URT infections also often precede the development of acute otitis media (AOM; i.e., middle ear infection). One longitudinal study sampled infants (<1 month to at least 6 months old) to the first episode of AOM and reports that the relative abundance of the otopathogen-containing genera *Moraxella* and *Streptococcus* increased during symptomatic viral infection (+/−AOM) compared to asymptomatic viral colonization and virus-free healthy samples [19]. Additionally, compared with controls, the NP microbiota of infants with more reported URIs in the first three to six months had increasing relative abundance of *Streptococcus, Moraxella* or *Haemophilus*. Also, increased relative abundance of *Staphylococcus* and *Sphingobium* was associated with a lower risk of AOM complicating URI [19].

In summary, the variation in findings between the above pioneering longitudinal studies (Table 1) illustrates the critical need for more and larger prospective longitudinal studies of infant nasal microbiota and ARI, ideally exploring host–microbiota–viral infection interactions and the relationship of these to severity of disease and risk for secondary bacterial infection.

Bacterial pathobiont infection and nasal microbiota

Colonization with the pathobionts *S. pneumoniae, H. influenzae* and *S. aureus* is associated with lower levels of bacterial microbiota diversity and decreased levels of commensals, indicating a potentially disturbed microbiota [19,31–35]. *S. pneumoniae* commonly colonizes the nasal passages of infants [36] and is an important cause of pediatric infection. Introduction of the pneumococcal conjugate vaccines (PCV) led to a profound decrease in invasive pneumococcal disease [37,38], and preceded the boom in culture-independent studies on nasal microbiota, thus there is limited data on relationships between *S. pneumoniae* and commensals in unvaccinated children. In post-PCV7 era studies, children with pneumococcal colonization have lower relative abundances of *Corynebacterium* and *Dolosigranulum* than children without [4,39]; *Lactococcus* is also negatively correlated with

the genus *Streptococcus* [39]. A longitudinal study sampling biweekly for the first year of life compared the effect of the 7- vs. 13-valent PCV vaccines on *S. pneumoniae* colonization and nostril microbiota composition. There were no differences in the density of pneumococcal colonization between the PCV7- and PCV13-immunized groups; however, more samples were positive for pneumococcus in the PCV7 group and microbiota had increased alpha diversity in the PCV13 group [40]. Recent studies are beginning to elucidate molecular mechanisms that might underlie the associations observed between pathobionts and commensals in nasal microbiota [1,3–7]. Knowledge of molecular mechanisms coupled with well designed longitudinal microbiota-based studies will set the field on the path from correlation to causation.

The transition to an adult-type nasal microbiota

Based on studies of either children or adults, it is evident that the bacterial composition of the nasal microbiota differs between these life stages. A cross-sectional study focused on this transition indicates that puberty has a major impact on nasal microbiota composition [41]. There are statistically significant differences in nostril microbiota composition with Proteobacteria (*Moraxella*, *Haemophilus* and *Neisseria*) and Firmicutes (*Streptococcus*, *Dolosigranulum*, *Gemella* and *Granulicatella*) overrepresented in prepubertal children, whereas Actinobacteria (*Corynebacterium*, *Propionibacterium* and *Turicella*) are overrepresented in adults [41].

Older adults: aging and the bacterial microbiota of the nasal passages

In comparison with early life, there are few studies on the nasal microbiota in older and elderly adults (Table 1). It remains to be determined if changes occurring within the aging body (e.g., immunosenescence) affect the composition of the nasal bacterial microbiota. A recent cross-sectional study characterizing the nasal and oropharyngeal bacterial microbiota of Canadian nursing home residents between the ages of 68–96 (mean 80) years revealed an oropharynx-like composition of the nostril microbiota dominated by non-pneumococcal *Streptococcus* suggesting a transition of the nasal microbiota in aging adults and a loss of microbial topography in the URT [42]. However, other studies have found no such change [43,44] and, in general, there is a lack of longitudinal data. In a recent Finnish case-control study investigating the nasal microbiota of Parkinson's disease (PD) patients with, frequency-matched for age and gender, healthy controls (mean age of healthy controls 64.4 years), the most abundant genera in both groups were *Corynebacterium*, *Propionibacterium*, *Moraxella*, *Staphylococcus* and *Burkholderia* followed by *Dolosigranulum*, *Pseudomonas*, *Simonsiella* and *Streptococcus* [44] resembling more the mid-aged adult nasal bacterial microbiota. Similarly, comparison of the bacterial nasal microbiota of nursing home residents and elderly living independently in the Baltimore area revealed no difference in diversity between the two groups [43]. There was, however, a difference in the relative abundance with *Lactobacillus reuteri*, *Streptococcus*, *Staphylococcus epidermidis* (all Firmicutes) and *Rothia mucilaginosa* (Actinobacteria) increased in nursing home participants [43]. As with infants, negative associations between commensal bacteria and pathobionts are reported. A Danish twin study—including mono- and dizygotic twins ages 50–79 years—found *Dolosigranulum pigrum* to be the most informative predictor of nasal *S.*

aureus colonization in a threshold-dependent manner and that host genetics is a minor determinant of *S. aureus* colonization [45,46]. In addition to the clear need for further studies of nasal passage microbiota in older adults, the implication that host genetics play a lesser role in microbiota composition suggests a role for future microbiota-directed therapies to prevent respiratory tract infection, and potentially modulate other diseases of the respiratory tract.

Gaps in Current Knowledge and Areas for Future Research

The rapid expansion of literature on the composition of the bacterial microbiota of the human nasal passages in health and acute infection reflects a growing recognition of the exciting possibilities for future microbiota-derived and microbiota-targeted approaches for both prevent and treat disease [47]. Below we highlight some of the key questions and gaps in knowledge.

For infants:

1. What is the interplay between the development of both the nasal bacterial microbiota and the host immune system?
2. Do transient differences in nasal microbiota based on route of delivery/feeding overlap with a critical window of development in host immunity resulting in long-term impacts on health?
3. Does development of nasal microbiota vary across socioeconomic, cultural and geographic regions?

For toddlers through teens:

1. Identify the composition of the nasal microbiota for school age, prepubertal children, as this is a notable gap in current data.
2. What mechanisms drive the changes in nasal bacterial community composition during puberty? [41]

For older adults, in whom studies on nasal microbiota are still surprisingly rare given the increased morbidity and mortality due to respiratory tract infections in this age group:

1. Do changes in the immune system during aging lead to changes in nasal microbiota?
2. Is there a loss of biogeographic variation in the bacterial microbiota between the nasal passages and oropharynx with aging?
3. Is the bacterial composition of URT microbiota associated with susceptibility to and/or severity of respiratory tract infections? A question best addressed through longitudinal studies.
4. What is the impact of menopause on nasal microbiota?

In addition to intriguing questions surrounding the relationship between the bacterial microbiota of the human nasal passages and infection, emerging literature also suggests

possible connections to other diseases such as asthma and chronic rhinosinusitis. We expect research on the human nasal microbiome to continue to expand rapidly and shift towards addressing questions of function and causation while maintaining a focus on disease-related questions.

Acknowledgments

We would like to thank Markus Hilty, Isabel Fernández Escapa and the reviewers for critical comments, which improved the manuscript, and Markus for his encouragement and helpful discussions. To colleagues whose work could not be cited due to space limitations or because it is too recent to have been in our search findings, we extend our sincere apologies.

Funding: This work was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health (R01GM117174 to KPL), the Swiss National Science Foundation (P3SMP3_155315 to SDB) and the Novartis Foundation for Medical-Biological Research (16B065 to SDB).

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Table 1

[a]Nasal bacterial microbiota studies included in this review[b].

Reference	First; last author surnames	Year	16S rRNA gene region	Sequencing platform	Age range	Country	Study population and risk group	Design
[8]	de Steenhuijsen Piters; Mejias	2016	V5-V7	454	<2 years	USA	Mild RSV vs. severe RSV vs. healthy	Cross-sectional
[10]	Biesbroek; Bogaert	2014	V5-V7	454	1–24 months	Netherlands	Healthy	Longitudinal cohort with cross-sectional validation groups
[11]	Biesbroek; Bogaert	2014	V5-V7	454	6 weeks and 6 months	Netherlands	Healthy (breast vs. formula fed)	Longitudinal cohort
[12]	Mika; Hilty	2015	V3-V5	454	5 weeks–12 months	Switzerland	Healthy	Longitudinal cohort
[13]	Teo; Inouye	2015	V4	illumina	2–12 months	Australia	High risk for atopy: Healthy and ARI	Longitudinal cohort
[14]	Shilts; Das	2016	V1-V3	454	5–140 days	USA	Healthy	Cross-sectional samples
[15]	Peterson; Graham	2016	NA (*cpn60*)	454	2 weeks–1 year and adult caregivers	Canada	Healthy	Longitudinal cohort
[16]	Bosch; Bogaert	2016	V4	illumina	0–6 months	Netherlands	Healthy	Longitudinal cohort
[17]	Bosch; Bogaert	2017	V4	Illumina	0–12 months	Netherlands	Healthy and ARI	Longitudinal cohort
[18]	Kelly; Seed	2017	V3	Illumina	1–23 months	Botswana	CAP, URI and healthy	Cross-sectional
[19]	Chonmaitree; Fofanov	2017	V4	Illumina	0–12 months	USA	Healthy and URI +/− AOM	Longitudinal cohort
[21]	Chu; Aagaard	2017	V3-V5	454	0–6 weeks and mothers	USA	Healthy	Longitudinal cohort and cross-sectional
[22]	Bogaert; Sanders	2011	V5-V6	454	18 months	Netherlands	Healthy	Cross-sectional
[24]	Hasegawa; Camargo	2016	V4	Illumina	<1 year	USA	Bronchiolitis hospitalized	Cross-sectional samples
[20]	Hasegawa; Camargo	2016	V4	Illumina	<1 year	USA	Bronchiolitis hospitalized vs. healthy	Cross-sectional samples
[29]	Rosas-Salazar; Hartert	2016	V4	Illumina	mostly ≤6 months	USA	ARI	Cross-sectional samples
[28]	Mansbach; Camargo	2016	V4	Illumina	<1 year	USA	Bronchiolitis	Cross-sectional
[27]	Korten; Latzin	2016	V3-V5	454	0–12 months	Switzerland	Healthy and URI	Longitudinal cohort
[31]	Pettigrew; Metlay	2012	V1-V2	454	6 months – 3 years	USA	URI, AOM and healthy	Cross-sectional
[32]	Hilty; Muhlemann	2012	V3-V5	454	<2 years	Switzerland	AOM and healthy	Cross-sectional
[33]	Brugger; Hilty	2012	8F-907R	T-RFLP	<2 years	Switzerland	AOM	Cross-sectional

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Reference	First; last author surnames	Year	16S rRNA gene region	Sequencing platform	Age range	Country	Study population and risk group	Design
[34]	Sakwinska; Gervaix	2014	V1-V2	454	2 months – 16 years	Switzerland	CAP vs. healthy (minor surgery)	Cross-sectional
[39]	Laufer; Pettigrew	2011	V1-V2	454	6 to 72 months	USA	Outpatient with URI symptoms	Cross-sectional
[4]	Bomar; Lemon	2016	V1-V3	454	>6 months – <7 years	USA	Outpatient pediatric visit	Cross-sectional
[40]	Mika; Hilty	2017	V3-V5	454	0–12 months	Switzerland	Healthy	Cohort/Longitudinal
[41]	Oh; Kong	2012	Full-length	Sanger	Prepubertal children, adolescents and adults	USA	Healthy	Cross-sectional
[42]	Whelan; Bowdish	201 4	V3	illumina	68–96 years	Canada	Nursing home	Cross-sectional
[43]	Roghmann; Mongodin	2017	V3-V4	Illumina	≥65 years	USA	Nursing home vs. community	Cross-sectional
[44]	Pereira; Scheperjans	2017	V1-V3	illumina	Older adults – elderly	Finland	Healthy vs. Parkinson's disease	Cross-sectional
[45]	Liu; Andersen	2015	V3-V6	454	50–79 years	Denmark	Healthy	Cross-sectional

[a] Abbreviations: RSV: respiratory syncytial virus ARI: acute respiratory tract infection; URI: upper respiratory tract infection; AOM: acute otitis media; NA: not applicable; cpn60: chaperonin-60 universal target; CAP: community-acquired pneumoniae

[b] Literature was screened by performing the following searches in NCBI's PubMed [www.pubmed.gov]: "human nasal microbiota"; "human nasal microbiome"; "human infant nasal microbiome and microbiota"; "human infant nasopharyngeal microbiome and microbiota"; "human nasal microbiota and microbiome"; "human nasopharyngeal microbiota and microbiome"; "adult nasal microbiota"; "elderly nasal microbiota"; "nursing home nasal microbiota"; "nasal microbiota human"; "pneumonia nasal microbiome"; "respiratory infection and nasal microbiome"; and "otitis media nasal microbiome". We then selected individual articles. The main goal was to identify primary research articles focusing on the nasal bacterial microbiota in healthy children and elderly as well as articles investigating the microbiota in health and acute respiratory infections in these age groups. Due to space limitation, we could not include work describing analyses of specific conditions such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), asthma and allergic rhinitis, interstitial lung disease, chronic rhinosinusitis and others, with an exception if there was a specific control group of interest for this review. We apologize to all the authors whose work was not included or which we may have missed despite a careful search and evaluation.

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