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Bacterial microbiota of the nasal passages across the span of human life

Lindsey Bomar[1,2,4], Silvio D Brugger[1,2,4] and Katherine P Lemon[1,3]

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.

Addresses
[1] The Forsyth Institute (Microbiology), Cambridge, MA, United States
[2] Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, United States
[3] Division of Infectious Diseases, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States

Corresponding author: Lemon, Katherine P (klemon@forsyth.org)
[4] These authors contributed equally to this work.

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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 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) [8,10,11,12••,13•,14–16,17••,18–20]. 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. A longitudinal study of western European infants, from birth to 6 months, reveals a common *Streptococcus*-enriched community

Table 1

Nasal[a] 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
[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	2014	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] 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 pneumonia.

[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.