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Review article

Review of human hand microbiome research

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ABSTRACT

Recent advances have increased our understanding of the human microbiome, including the skin microbiome. Despite the importance of the hands as a vector for infection transmission, there have been no comprehensive reviews of recent advances in hand microbiome research or overviews of the factors that influence the composition of the hand microbiome.

A comprehensive and systematic database search was conducted for skin microbiome-related articles published from January 1, 2008 to April 1, 2015. Only primary research articles that used culture-independent, whole community analysis methods to study the healthy hand skin microbiome were included.

Eighteen articles were identified containing hand microbiome data. Most focused on bacteria, with relatively little reported on fungi, viruses, and protozoa. Bacteria from four phyla were found across all studies of the hand microbiome (most to least relative abundance): Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes. Key factors that impacted the hand microbiome composition included temporal and biogeographical dynamics, as well as intrinsic (age, gender) and extrinsic (product use, cohabitants, pet-ownership) variables.

There was more temporal variability in the composition of the hand microbiome than in other body sites, making identification of the "normal" microbiome of the hands challenging. The microbiome of the hands is in constant flux as the hands are a critical vector for transmitting microorganisms between people, pets, inanimate objects and our environments. Future studies need to resolve methodological influences on results, and further investigate factors which alter the hand microbiome including the impact of products applied to hands. Increased understanding of the hand microbiome and the skin microbiome in general, will open the door to product development for disease prevention and treatment, and may lead to other applications, including novel diagnostic and forensic approaches.

Contents

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1. Introduction

Human skin is the first layer of defense against infectious microorganisms and toxic agents. Skin is the largest human organ, and is a dynamic environment; constantly impacted by internal factors and exposed to external conditions. These intrinsic and extrinsic factors can alter the microbial community on the skin [1]. Until recently, skin microbiology was limited to culture-dependent studies, with most samples from pathologies [2]. However, non-pathological bacteria are detected everywhere on humans, with up to 1×10^7 bacteria per cm^2 on the skin [3]. Although the culture-based approach is still common, many microorganisms are difficult to cultivate and are therefore under-represented or undetected in culture-based surveys. The availability of cost-effective and high-throughput culture-independent methods, including 16S rRNA gene sequencing and advanced bioinformatics, has significantly improved our understanding of the human microbiome [4,5]. An advantage of targeting the 16S rRNA gene is that it is universal in bacteria, and allows sequences between organisms to be compared at various levels of taxonomic resolution in contrast to culture-based classification which is limited to morphological and phenotypical classification [6]. Other approaches, including metagenomics are used to capture the full range of diversity in the microbiome, including fungi, viruses and protozoa [7]. To date many studies of the human microbiome have focused on the gut and oral microbiomes. There are increasing numbers of skin microbiome studies, however, sampling has rarely focused on the hands [8,9]. Our knowledge of the hand microbiome and factors that impact it are still primarily limited to culture-based studies.

Human hands are a conduit for exchanging microorganisms between the environment and the body. Hands can harbor pathogenic species, including methicillin-resistant *Staphylococcus aureus* (MRSA) or *Escherichia coli*; particularly within high risk environments, such as healthcare and food-handling settings [10]. Product use can impact the hand microbiome, with greater pathogen hand carriage on people using a high level of hand hygiene products, while other studies have demonstrated reduced pathogen carriage and/or infections with use of these products. Frequently washed hands of healthcare workers are colonized with more pathogenic bacteria than those who wash less frequently [11]. Hand washing with soap dispensed from open bulk-refillable dispensers was shown to increase the levels of opportunistic pathogens on childrens' hands in an elementary school [12]. However, many studies have demonstrated the beneficial impact of hand washing and/or use of alcohol-based hand rubs for reducing pathogenic bacteria on hands and/or reducing infection rates in various institutional settings [13–15]. The occurrence of pathogens on hands is well-studied; in contrast, hands are rarely considered a source of beneficial bacteria contributing to our healthy microbiome.

Since hands are important for intrapersonal and interpersonal transfer of microorganisms, as well as environmental transfer, the dynamics of hand microbial communities and factors impacting them are of considerable importance [16]. Key topics include understanding the normal microbiome of healthy hands, how microbes are transferred by hands, what factors impact the hand microbiome, and whether those impacts are beneficial or detrimental to human health. This is the first review of hand microbiome studies. Most microbiome studies have focused on detecting bacteria, fewer have determined what fungi, viruses or protozoa were present. Therefore, this review is focused on the hand-associated bacterial communities, but will mention other organisms where data are available. Additionally, the authors will highlight the importance of hands as a critical vector in microbiome dynamics.

2. Methods

The database search was performed using PubMed, ABI/INFORM Professional, BIOSIS Previews, British Library Inside Conferences, Current Contents Search, Embase, Embase Alert, Gale Group Health Periodicals Database and PharmaBioMed Business Journals, Global Health, International Pharmaceutical Abstracts, Lancet Titles, Medline, The New England Journal of Medicine, PASCAL, and SciSearch®. Search terms were: hand and/or skin microbiome, skin metabolome, hypothenar palm microbiome, epidermal microbiome, cutaneous microbiome, stratum corneum bacteria.

Fig. 1 shows a schematic of article selection criteria. The search resulted in >600 peer-reviewed articles published from 1/1/2008 through 4/1/2015. Articles were selected for review based on the requirement for culture-independent and whole community analysis methods to characterize the human skin microbiome. Articles in the review were further refined by including only primary research articles that studied the healthy hand microbiome.

3. Results

3.1. Overview of hand microbiome studies

Table 1 summarizes the 18 articles that met all search criteria, and provides an overview of methods for each study. Samples for microbial analyses were typically collected by swabbing the hand

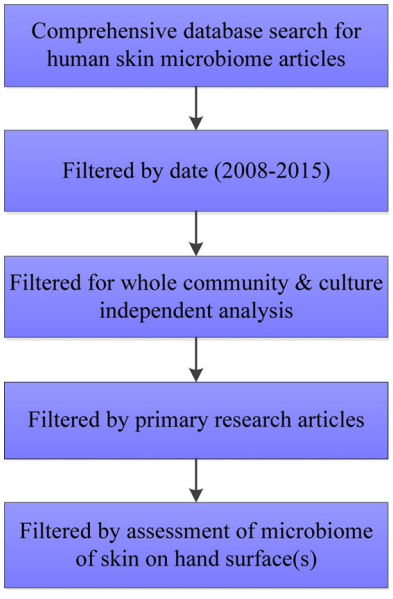

Fig. 1. Schematic of process for selection of articles.

Table 1
Summary of study methods for articles assessing the hand skin microbiome..

Reference	Skin sampling method	Setting	Subjects' age, gender, and ethnicity	*N*	# Repeat samples	Sampling duration	Area of hand(s) sampled	Non-hand site(s) sampled	16S rRNA gene survey amplification region(s)	Other microbiome characterization method(s) or metadata
Bouslimani et al. [21]	Swab	University of California, San Diego	Healthy subjects, a male and a female	2	2	Not specified	Front and back	~400 other skin sites	V3–V5	UPLC-QTOF MS, MALDI-TOF, 3D Modeling
Caporaso et al. [22]	Swab	Boulder, CO	Healthy subjects, a male and a female	2	>396	Daily; Male for 15 months, female for 6 months	Palms	Stool, oral	V2, V4–V5	N/A
Costello et al. [24]	Swab	Boulder, CO	Healthy adults of both sexes, ages 30–60	9	4	2 consecutive days, 2×, 3 months apart	Palms and index fingers	Hair, nose, ear, oral, stool	V1–V2	N/A
Fierer et al. [17]	Swab	Boulder, CO	Healthy students of mixed gender	51	1	N/A	Palm	N/A	V1–V2	N/A
				8	3	Handwash Pilot: every 2 h for 6 h				
Fierer et al. [33]	Swab	Boulder, CO	Healthy adults of mixed gender, ages 20–35	Key-board: 3	1	N/A	Fingertips (ventral surface of distal joint)	Armpit, keyboard keys, computer mouse	V1–V2	N/A
				Mouse: 9	1	N/A	Palms			
Findley et al. [19]	Swab and skin scraping	Washington DC Area	Healthy adults ages 18–40	18	1–2	Subset of subjects sampled 1–3 months post initial sample	Left and right hypothenar palm	13 other skin sites	V1–V3	18S rRNA and ITS1 amplicon sequencing
Flores et al. [23]	Swab	University of Colorado Boulder, Northern Arizona University, North Carolina State University	College students	85	>10	Weekly for 10 week minimum	Palms	Forehead, oral, stool	V4–V5	Weekly survey of demographic, lifestyle and health information
Grice et al. [25]	Swab and skin scraping	Washington DC area	20–41 y/o	10	2	4–6 month after initial sampling	Hypothenar palm and interdigital web space, both hands	18 other skin sites	V1–V9	N/A
Hospodsky et al. [32]	Glove juice	U.S. and Tanzania	Adult females	44	1	N/A	Whole hands	N/A	V3–V5	N/A
Lax et al. [16]	Swab	Houses in Illinois, Washington and California	Unknown	15 adults, 3 children	>20	Every other day for 6 weeks	Unknown	Nose, home surfaces, pets	V4–V5	Shotgun sequencing
Mathieu et al. [2]	Swab	Unknown	Caucasian males, ages 25–26	2	Every two days	One week	Palm	Face, axilla, feet, and retro auricular crease	Unknown	Functional classification of genes based on reference metagenomic databases
Meadow et al. [30]	Swab	Princeton, NJ	Adults	17	1 time point	N/A	Thumb and index finger	Cell phone	V4–V5	N/A
Nakatsuji et al. [28]	Surgical biopsy	San Diego, CA	2 males and 1 female ages 53–69	11	1	N/A	Palm (cut from the dermis to the epidermis)	Face	V6–V7, gene-specific primers	Immunostaining, laser capture microdissection

Table 1 (*Continued*)

Reference	Skin sampling method	Setting	Subjects' age, gender, and ethnicity	*N*	# Repeat samples	Sampling duration	Area of hand(s) sampled	Non-hand site(s) sampled	16S rRNA gene survey amplification region(s)	Other microbiome characterization method(s) or metadata
Oh et al. [20]	Swab/scrape/ swab technique	Washington DC	9 males and 6 females, ages 23–39	15	1	N/A	Hypothenar palm and interdigital web space	16 other skin sites	V1–V3	de novo identification, reference base strain mapping
Rosenthal et al. [18] (Pathogens)	Swab and glove juice	University of Michigan Hospital SICU	Healthcare workers, mostly female, caucasian, born in US, ages 20–59	34	3	Weekly for 3 weeks	Palm, fingertips, and in-between fingers	N/A	V6	18S rRNA gene survey; participant survey and visual hand skin assessment
Rosenthal et al. [26] (PLOS ONE)	Swab and glove juice	University of Michigan Hospital SICU	Healthcare workers, mostly female, caucasian, born in US, ages 20–59	34	3	Weekly for 3 weeks	Palm, fingertips, and in-between fingers	N/A	V6	N/A
Smeekens et al. [31]	Swab	Netherlands	Healthy controls; chronic muco-cutaneous candidiasis and hyper-IgE syndrome patients	11 case; 10 control	1	N/A	Unknown	Feet, trunk and oral	V4–V5	Immunological in vitro stimulations assays to identify genetic potential defects
Song et al. [29]	Swab	Households	Couples, age 26–87, and children (6 months–18 years)	159	1	N/A	Palms	Forehead, oral, stool, dogs	V2	N/A

surface. For studies that utilized 16S rRNA gene sequencing, investigators used a variety of gene regions for sequencing. Overall, the data on hands is limited compared to other body sites, and the majority of studies were conducted on young adults, often students or professionals, in the United States. Most studies contained a small sample size ($\leq$10) and/or assessed microbial composition at a single time-point.

3.2. Microbiome of the hands

Eleven studies in this review characterized the relative abundance of bacteria on hands, and findings are summarized in Table 2. Table 2 displays bacteria families found at 1% or greater relative abundance. Most studies reported between 8 and 24 families of bacteria on hands. Bacteria were found from four phyla across all studies (most to least relative abundance): Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes. There were considerable differences in the types of bacteria found among the studies, with Staphylococcaceae, Corynebacteriaceae, Propionibacteriaceae and Streptococcaceae being found in a majority of the studies. Interestingly, Propionibacteriaceae, when detected, was often quite high in relative abundance.

The first study of the hand microbiome demonstrated there are on average >150 bacterial species found on the palms, with 3 phyla accounting for >94% of sequences: Actinobacteria, Firmicutes and Proteobacteria [17]. A study evaluating the hands of healthcare workers found those with less microbial diversity were more likely to harbor pathogenic microorganisms on the hands, such as *S. aureus* (including MRSA), *Enterococcus* spp., or *Candida albicans* [18]. One study evaluated both fungal and bacterial diversity on the hands and found *Malassezia* spp. were the most common fungal inhabitants, with *Aspergillus* spp. the second most common [19]. Bacteria were the most prevalent microorganism (>80% relative abundance), then viruses, and fungi being least prevalent (<5% relative abundance) on hands [20]. However this finding may be somewhat biased for greater proportion of bacteria, since the relative size of viral genomes is small, and would therefore be expected to represent proportionally less of the sequence data, even if bacteria and viruses were equally abundant.

3.3. Metabolic functions of the hand microbiome

Three studies reviewed used culture-independent metabolomic techniques to investigate the functional (metabolic) role of the skin microbiome, including hands. Mathieu et al. [2] evaluated the functional characteristics of the hand microbiome, however samples were pooled from multiple time points and skin sites so conclusions that are specific to hands are impossible. Overall, their findings indicated key functions of the skin microbiome, including uptake of sugars, lipids, iron, and the catabolism of lactic acid [2]. Other functional genes were associated with acid resistance and regulation of skin pH; indicating skin microbes regulate functions with implications for skin health [2]. Oh et al. [20] evaluated the functional diversity of microbial communities at different skin sites, finding a predominance of citrate cycle modules in communities inhabiting dry sites, including palms. There were also general biomolecular and metabolic functions common across several body sites [20]. Bouslimani et al. [21] used a novel approach, mapping the metabolic components over time for many body sites, including hands, providing a map of temporal and biogeographical changes to metabolic constituents. Combining this with bacterial genomic and biochemical data from beauty products showed that daily routines, particularly product use, have a large impact on our metabolomic identity [21]. Overall, it appears the functional component of the metagenome (the genomic contents of an entire microbial community) varies widely, which is not unexpected given the wide variation in the taxonomic composition of communities [20].

3.4. Temporal dynamics of the hand microbiome

Next, we investigated how the microbiome of the hands changes over time, and Caporaso et al. [22] provided the most comprehensive study of how an individual's hand microbiome changes over time. In this study, one female and one male participant were each sampled daily for 6 and 15 months, respectively [22]. Their findings showed hand microbiome composition fluctuated, however there were persistent community members that showed up in most samples, with varied relative abundance at any given sampling time [22]. Persistent community members on hands included Actinobacteria, Bacteroidia, Flavobacteria, Sphingobacteria, Cyanobacteria, Bacilli, Clostridia, Fusobacteria, Alphaproteobacteria, Betaproteobacteria, and Gammaproteobacteria [22]. Another study showed there is a persistent community for some individuals, and found that relatively abundant and persistent members include taxa within Actinobacteria, Bacilli, and Gammaproteobacteria [23]. Skin, including palms, harbored a characteristic microbiome over time, with less variation over 24-h than a 3-month period [24]. Not surprisingly, it was generally demonstrated that interpersonal hand microbiome variation is greater than temporal variation [24–26]. However, temporal variation on the hands is quite high with <15% of phylotypes being found over multiple sampling periods, and even for those phylotypes that are found at multiple time points there can be substantial changes in their relative abundances [23]. This high variability may be driven by higher abundance of transient organisms present at any given time-point [23]. Additionally, time of sampling (days to months apart) did not significantly correlate with microbiome composition, indicating that the hand microbiome does not change in a predictable manner over time [23].

3.5. Biogeographical dynamics of the hands compared to other body sites

Skin biogeography significantly impacts the composition of the microbiome, twelve studies that evaluated the hands and other skin sites determined that the hands have a unique microbiome. Hands have greater bacterial diversity; and the hand microbiome is more dynamic over time than other skin sites [22–24,27]. Palm skin typically harbors >3 times more bacterial phylotypes per individual compared to forearm or elbow skin [25,27]. Fungal species diversity was intermediate on hands, with feet having greater diversity and core body skin sites having the least diversity [19]. Microbial communities on hands were generally enriched with different bacterial taxa compared with other body sites [17,18,24,25], and acquired a larger pool of total bacterial species through time [23]. The interpersonal variation of the hand microbiome was less than the variation between different body sites on the same individual [24,25]. Temporal stability of the microbiome is dependent on physiological conditions of the skin; with moist, warm, and nutritionally rich skin sites harboring a more stable microbiome than hands which are dry and continually exposed to varying environments [22,27]. Additionally, individuals with more variable hand bacterial communities have greater variability at other skin sites, indicating microorganisms may be transferring between skin sites [23].

Not only does the microbiome vary with geographical body location, but the layers of skin at different depths may harbor compositionally distinct microbiomes. The impact of skin depth was exhibited by the significant difference in the microbiome observed between identical samples obtained with glove juice

Table 2
Summary of relative abundance* (in percent) of microorganisms found on hands at family level..

Phylum	Class	Order	Family	Bouslimani et al. [21]	Caporaso et al. [22]		Costello et al. [24]	Fierer et al. [17]	Findley et al. [19]	Flores et al. [23]	Grice et al. [25]	Hospodsky et al. [32]		Meadow [30]	Oh et al. [20]	Song et al. [29]			
					Persistent	Transient						US	Tanzania			Infant	Child	Adult	Senior
Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	0.5			1.3			1.8		2.0		2.0					
			Corynebacteriaceae	3.3			2.4	4.3	7.7	10.5	10.4	2.1		23.6	4.6		3.0	4.2	4.3
			Nocardiaceae										12.4						
			Intrasporangiaceae	1.1															
			Micrococcaceae	1.7			3.7		1.7	2.9		14.4	7.6		2.0	4.7	3.9	2.8	2.7
			Propionibacteriacea				37.4	31.6	47.8		15.4	15.2			3.9	3.1	11.0	27.0	20.0
	Other (within Phylum)			3.4	21.3	18.6		6.1	1.3						2.7				
Bacteroidetes	Bacteroidetes	Bacteroidales	Bacteroidaceae		2.1	5.3											1.6	1.6	3.4
			Porphyromonadaceae							1.1						2.0	1.9	1.4	
			Prevotellaceae				1.1	1.0	1.6	2.0						5.6	4.2	3.1	2.1
	Flavobacteria	Flavobacteriales	Flavobacteriaceae			2.6	1.8		1.7	1.2	10.8		3.4			1.0	1.9	2.7	3.8
	Sphingobacteria	Sphingobacteriales	Sphingobacteriaceae			2.5						2.4							
	Other (within Phylum)														27.0				
Firmicutes	Bacilli	Bacillales	Bacillaceae	9.7						1.0			6.5	1.2					
			Exiguobacteraceae										2.2						
			Gemellaceae									1.1							
			Planococcaceae										2.2						
			Staphylococcaceae	1.7			3.6	8.3	12.2	11.2	8.5	28.2	4.5	24.7	8.7	3.2	5.1	6.7	2.8
			Other (within Order)		35.7	10.0													
	Coccus	Lactobacillades	Carnobacteriaceae	3.9										1.3		6.4	5.0	1.7	1.0
			Streptococcaceae	3.7			8.3	17.2	7.6	11.7		15.1		27.3		49.0	27.0	15.0	13.0
			Aerococcaceae					1.6											
			Lactobacillaceae					4.1		4.2	5.8	7.1		3.1				1.5	4.2
	Clostridia	Clostridiales	Acidaminococcaceae					1.1											
			Clostridiaceae	1.7	6.5	9.4				3.3									
			Lachnospiraceae				1.6			1.0								1.0	3.1
			Peptostreptococcaceae					1.2											
			Veillonellaceae				2.1			1.6				2.2		5.5	2.2	1.7	1.9
			Other (within Order)				2.0				2.5						1.5	1.0	1.4
		Other (within Phylum)		18.4				1.5							3.1				
Proteobacteria	Alpha-proteobacteria	Caulobactereales	Caulobactereaceae										3.0						
		Rhodospirillales	Acetobacteraceae						1.6										
		Rhodobacterales	Rhodobacteriaceae										21.0						
		Rhizobiales	Bradyrhizobiaceae					1.2					4.5						
			Brucellaceae									4.6							
			Rhizobiaceae										4.0						
		Sphingomonadales	Sphingomonadaceae				1.1			1.0		1.1	3.2						
			Other (within Order)																
		Other (within Class)		4.2	1.2	6.3				1.1	1.8								
	Beta-proteobacteria	Burkholderiales	Comamonadaceae									4.0						1.5	3.6
			Other (within order)					3.1		1.0			12.7						
		Neisseriales	Neisseriaceae					2.3	3.8	2.0		1.4		4.8		2.6	3.5	1.6	2.0
		Other (within Class)		1.5	3.4	12.1					22.8								
	Gamma-proteobacteria	Aeromonadales	unknown							1.1									

	Enterobacteriales	Enterobacteriaceae						1.2											
	Pseudomonadales	Pseudomonodaceae	1.4			1.3		3.8									1.1	2.4	
		Moraxellaceae				1.6	2.7	4.5			2.4		2.4		1.5	1.2	3.2	3.3	
	Pasteurellales	Pasteurellaceae	4.0			1.1	1.5	3.7					5.7		2.6	4.4	1.8	1.2	
	Xanthomonodales	Xanthomonadaceae						1.3		12.1	1.8								
	Other (within Class)		1.0	10.1	25.7				13.9										
												47.9							
	Other (within Phylum)			2.5	3.6									1.6	1.8	1.4	1.0		
Fusobacteria	Fusobacteriaceae																		
Other	Chloroflexi		13.4																
	Chloroplasts					11.7	1.6												
	Cyanobacteria		2.9	16.6															
	Streptophyta								7.3		5.8								
	Other																		

* Microorganism families with % relative abundance below 1.0 were not included in this table.

sampling and swabbing; indicating that deeper layers of the epithelium (contained in glove juice) contain a microbiome that is different from that obtained at the surface (swab) [26]. Additionally, Nakatsuji et al. [28] found bacteria in sub-epidermal compartments of palm skin to have distinct bacterial communities compared to those found on exposed areas of skin.

3.6. Intrinsic factors impacting hand microbiome composition

Two studies investigated the impact of age on the hand microbiome with mixed results. One found no impact of age on the hand microbiome, however all subjects in the study were adults, ages 20–59 [26]. Another study that evaluated a wider age range showed an insignificant effect of age on hand microbiome diversity and composition; however there were shifts in the relative abundance of organisms with the hands of infants and children having greater proportions of Firmicutes (including Carnobacteriaceae, Streptococcaceae, and Veillonellaceae), and the hands of adults and the elderly having higher proportions of Propionibacteriaceae [29].

Three studies investigated gender impacts on the hand microbiome composition, and overall men and women harbor distinct bacterial communities. One study showed significant gender effects on the hand microbiome, with Propionibacteria and Corynebacterium, more abundant on male hands, and Enterobacteriales, Moraxellaceae, Lactobacillaceae and Pseudomonaceae more abundant on female hands [17]. The palms of women had a more diverse bacterial composition than those of men [17,29]. This finding was further supported by studies showing a significant difference in the composition of the bacterial microbiome of the hands of adult males versus females [29,30]. Gender differences were also observed with interactions with inanimate objects, as the bacterial composition of female hands was significantly more like their mobile phones, than the similarity in bacterial composition of male hands to their phones [30].

Immune function and other health factors likely impact the bacterial composition of hand skin. A study found different bacterial composition on the hands of healthy controls compared with those of immune-compromised individuals; with healthy populations having greater proportions of *Staphylococcus* spp., *Fusobacterium* spp. and *Prevotella* spp., and the immune-compromised having a greater proportion of *Acinetobacter* spp. [31].

Only one study investigated whether a person's dominant hand had an impact on the bacterial community of the hand [17]. They found significantly more Lactobacillaceae, Enterobacteriales, Peptostreptococcaceae, and Xanthomonadales on the dominant hand [17]. However this difference may be indicative of an extrinsic, environmental impact since the dominant hand is more likely to be picking up transient microorganisms from the surrounding environment.

3.7. Extrinsic factors impacting hand microbiome composition

No studies in this review directly evaluated the impact of hand hygiene or other product use on the hand microbiome; however via self-reported survey data, researchers attempted to correlate hand hygiene practices, including the type of products used and the frequency of use, to changes in the hand microbiome. Healthcare workers likely have greater exposure to hand hygiene products than the rest of the population; however the overall microbial diversity on hands was unchanged with alcohol-based hand rub use or hand washing, with the exception that overall diversity was lower in those that reported >40 hand washing with soap and water events per shift [18]. The length of time since the last hand washing event impacted bacterial composition, with Propionibacteria, Neisseriales, Burkholderiales and Pasteurellaceae more

abundant with time since hand washing, and Staphylococcaceae, Streptococcaceae, and Lactobacillaceae more abundant on recently (<2 h) washed hands [17]. While there were changes in bacterial composition with time since last hand washing, there was no impact on the overall level of diversity on the hands [17]. Another study found no impact on hand microbiome composition when hand washing occurred within 1 h of sampling [30]. Frequency of hand washing on the day prior to sampling did not correlate with changes in bacterial composition [32]. Use of other topical products was not studied on hands, but use of oral antibiotics had a significant impact on the hand microbiome, with the largest shift observable around the time of use [23].

Those who live within the same home have a more similar hand microbiome than people who live in different homes; and couples and their young children share more bacterial taxa than unrelated roommates [16,29]. Additionally, owning a pet resulted in a significant increase in shared microorganisms for people within a household, and a person's hand microbiome is more like their own pet's paws than that of a pet in another household [29]. Additionally, pet ownership increases the overall diversity of bacteria on the hands [29].

Interaction with inanimate objects is another source of variability in the hand microbiome. A home becomes colonized with its occupant's microbiome, and for the majority of hand samples, the microbiome could be matched to light switches in their homes, indicating hands are a key vector for microbial contamination of surfaces within the home [16]. However, there are differences between the human microbiome and the microbial communities found inside our homes, with Firmicutes and Actinobacteria being more abundant on human skin relative to surfaces in the home [29]. Personal possessions such as cell phones and keyboards are another source of microorganisms, and studies have even shown that objects can be identifiable to their owner [30,33] which could make microbiome analyses of personal objects an alternative to human DNA forensic analyses.

Significant differences based on lifestyle and/or ethnicity were observed between the hand microbiome of Tanzanian mothers versus American female graduate students [32]. Rhodobacteraceae, Nocardioidaceae and Burkholderiales were enriched on Tanzanian hands; whereas Staphylococcaceae, Propionibacteriaceae, Streptococcaceae, and Xanthomonadaceae were more abundant on hands of students in the United States [32]. Interestingly, Rhodobacteraceae and Nocardioidaceae are typically found in soils and the aquatic environment, indicating Tanzanian women, who have close contact with the outside environment, acquire these bacteria in greater proportions than American women who primarily stay indoors [32].

4. Discussion

The hand microbiome was more variable and less stable over time than the microbiomes of other skin sites [17,22]. This dynamic and relatively unstable nature makes it difficult to conclude what is a "normal" or "healthy" hand microbiome. Also, most studies that evaluated the microbial composition of hands were looking at a single point in time. However, as day to day variation in hand microbiome composition can be quite high, a single time-point may not be representative, demonstrating the importance of sampling individuals over time to elucidate a "core" microbiome. As evident from Table 2, there is a high degree of variability in the composition of the hand microbiome across studies, variability that is at least in part related to different study populations, sampling strategies, and sequencing approaches. For example, Propionibacteriaceae were nearly always found in relatively high abundance when they were present, but were only present in samples from about two-thirds of studies, which may be a methodological artifact since some primers are biased against Propionibacteriaceae. It is known from previous studies that bacteria from the families of Staphylococcaceae, Streptococcaceae, Corynebacteriacea, and Moraxellaceae are common residents; therefore it was not surprising that most studies found organisms from these families. Lactobacillaceae, which tend to be anaerobic, were found in nearly all studies, it is possible these bacteria are transients on the hands of females, being repopulated from resident vaginal populations.

There are many sources of variability, both intrinsic and extrinsic, that influence the hand microbiome composition. Skin physiology, which is impacted by both intrinsic factors (e.g. disease, immune function, age) and extrinsic factors (e.g. temperature, humidity, exposure to chemicals), has been shown to impact the composition of the skin microbiome [1,34]. Therefore, it is reasonable to hypothesize that any health or environmental condition that impacts hand skin physiology may affect the hand microbiome. Even the hand microbiome of the same individual when sampled at multiple time points can exhibit significant variation [22]. Age, handedness, and gender were intrinsic factors that impacted the composition of the hand microbiome [17,29]. Extrinsic factors, including cohabitation, familial relationships, and pet ownership, as well as interaction with fomites and our external environment also impacted the hand's microbial composition [16,30]. Considering the various surfaces our hands touch in a typical day it is not surprising that hands exhibit such high variation in microbial composition. Hands are like a busy intersection, constantly connecting our microbiome to the microbiomes of other people, places, and things. We therefore propose a model (Fig. 2), depicting hands as the critical vector for populating and repopulating the microbiome. Lax et al. [16] conducted a Bayesian network analysis that demonstrates hands as key vectors for transferring microbes to various body sites, pets and inanimate objects within homes, which provides further support for our model. Additionally, numerous culture-based studies have highlighted hands as a vector for transmission of microorganisms, including viruses [35–38]. Hands are an important vector in populating the human microbiome, therefore future skin microbiome studies should include hand sampling, as knowledge of the hand microbiome is critical for understanding overall human skin microbiome dynamics. Additionally, there is very little known about the microbiome of diseased hand skin (e.g. hand eczema, atopic dermatitis or psoriasis); therefore future studies should also include investigation of differences between healthy and diseased hand skin to further our understanding of what residents and/or functional components of the microbiome are important to maintain healthy skin. These studies could lead to interventions for the prevention and/or cure of these common skin ailments.

One limitation of this review was our inability to make quantitative comparisons across studies due to numerous differences in test methods and presentation of data as well as the paucity of data on microorganisms other than bacteria. There are no standardized test methods for sampling, assessing or reporting of microbiome data. However, a recent publication outlines critical steps in conducting a microbiome study, and adoption of their recommendations would increase the comparability of studies [39]. To minimize methodological sources of variability, we need standardized test methods similar to those that have been developed in other areas of research by organizations such as ASTM International. The methods employed in a study can significantly impact results, and several studies included in this review examined specific methodological differences. In the following paragraphs we propose several methodological recommendations for future hand microbiome studies.

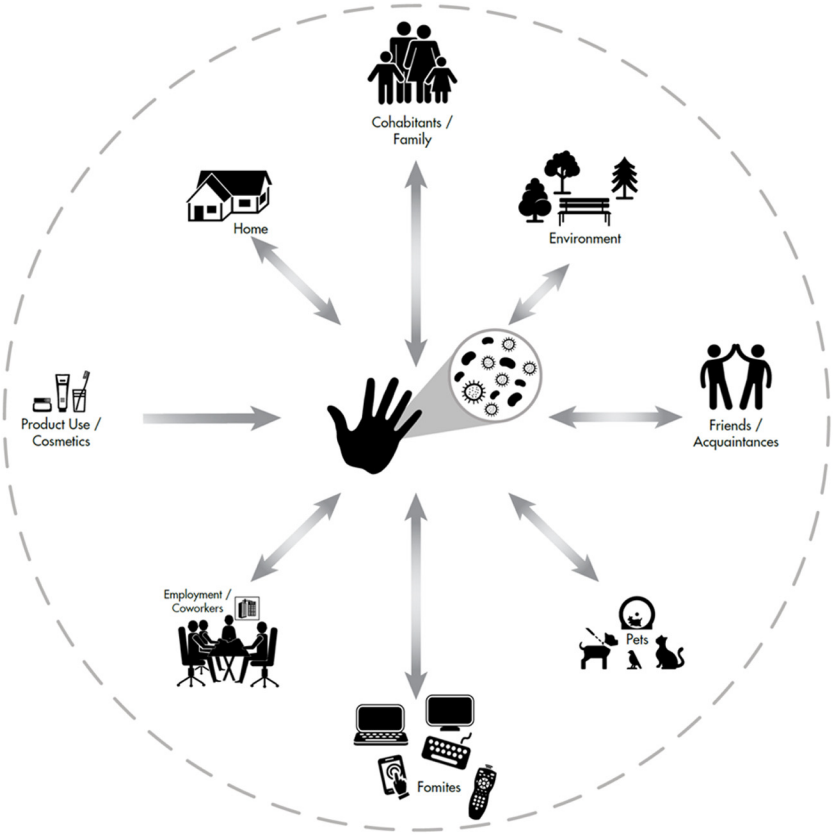

Fig. 2. Proposed model for the hand as a critical vector in microbiome dynamics.

Not all studies included a pre-wash to remove transient organisms before sampling; therefore a significant proportion of microorganisms studied may have been transient taxa. This limits our ability to make conclusions about the stability of communities on hands and whether particular microorganisms are more like to be transient or residents. This also makes it difficult to determine causal relationships between interventions on hands and their impact on hand microbiome composition. Therefore, we propose that hand sampling studies focused on the resident microbiome have test participants undertake a prewash with non-antimicrobial soap to remove transients prior to sampling.

The skin sampling methods used in the studies in this review were of 4 types: punch biopsy, glove juice, scrapping or swab (most to least invasive). Nearly all studies used the swab method to assess microbial composition. No differences were found in the types of bacteria found between swabbing and scraping [8], however there were significant differences between swabbing and glove juice sampling methods [26]. Swabbing only samples the skin surface where the swab touches, whereas the glove juice method samples the entire hand and is more aggressive, exposing more of the epithelial skin layers. Therefore, we should consider the possibility that data solely from swabs may overestimate the transient nature of the hand microbiome; since swabbing does not access microbes present in the deeper layers of skin which may house resident microbes that are likely more stable over time. Therefore, we propose the glove juice sampling method be used in combination with swabbing or in place of swabs for assessing the hand microbiome.

Current studies relied on self-reported data collected in surveys for assessing the impact of product use on the hand microbiome. Self-reported data can be inaccurate [40], therefore future studies that investigate the impact of products or other interventions on the hand microbiome should not rely solely on self-reported survey data but should be conducted in controlled laboratory-based settings or be case-controlled clinical studies.

Most studies in this review focused on young adults (typically professionals or students) in the United States. Additionally, the sample size for most studies was quite small. This makes it difficult to interpret results and generalize to other populations. It is recommended that future studies attempt to enroll a broader diversity of test participants to make results more generalizable.

Finally, only three studies in this review focused on the function of constituents of the microbiome. As we advance our understanding of microbiome dynamics, it will be critical to improve our understanding of the functional aspects of the microbiome using metabolomics and other emerging technologies. Emerging technologies are increasing our ability to mine databases to determine function of unknown metabolites; and tools are being developed that enable linkage of metabolite (and functional) data to specific microorganisms [21]. Therefore, the determination of key microbiome functions and how they can be manipulated will likely lead to new diagnostic approaches and new strategies for managing the hand microbiome.

As the scientific community embraces emerging technologies it is only a matter of time before products are developed that could change the hand microbiome composition for improved health outcomes or to assist in repopulating our microbiome after antibiotic use and/or illness. It is possible that assessing our hand microbiome at any given point in time could provide us with valuable information about our health status and/or environment which could lead to the use of our hand microbiome as a diagnostic tool and preventive health measure. Given the individual nature of our hand microbiome [33,41], using the hand microbiome and comparing it to surface microbiomes could become common as a

forensic application even more powerful than human DNA analysis. Our hands influence the microbiome of every surface we touch, leaving and picking up microbes with each touch. Using standardized methods and conducting larger studies in more populations will increase our understanding of the normal microbiome of hands, how it can be manipulated, and the impact of manipulation on health outcomes.

In conclusion, the hands are a critical component of the human microbiome. This is an area of study that has been underrepresented in the scientific literature, and we strongly recommend an increased focus on hand microbiome and metabolomics studies, in order to better address the question, "What is a healthy hand microbiome"?

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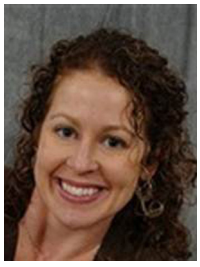

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