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Review

Non-pathogenic *Neisseria*: members of an abundant, multi-habitat, diverse genus

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The genus *Neisseria* contains the important pathogens *Neisseria meningitidis* and *Neisseria gonorrhoeae*. These Gram-negative coccoid bacteria are generally thought to be restricted to humans and inhabit mucosal surfaces in the upper respiratory and genito-urinary tracts. While the meningococcus and gonococcus have been widely studied, far less attention has been paid to other *Neisseria* species. Here we review current knowledge of the distribution of commensal *Neisseria* in humans and other hosts. Analysis of the microbiome has revealed that *Neisseria* is an abundant member of the oropharyngeal flora, and we review its potential impact on health and disease. *Neisseria* also exhibit remarkable diversity, exhibiting both coccoid and rod-shaped morphologies, as well as environmental strains which are capable of degrading complex organic molecules.

INTRODUCTION

The first description of a member of the genus *Neisseria* was in 1879 when Albert Neisser observed small diplococci within cells in urethral exudates of 26 men and women with gonorrhoea and from individuals with conjunctivitis (Neisser, 1879). Reliable isolation of the gonococcus only became possible once specific medium had been designed in 1885 by von Bumm (von Bumm, 1885). It took several years and several human challenge experiments before it was universally accepted that the gonococcus was responsible for gonorrhoea. *Neisseria meningitidis* was isolated from the cerebrospinal fluid of patients with meningitis by Weichselbaum in 1887 (Weichselbaum, 1887); he injected purulent meningeal fluid into the subdural space of animals to reproduce the clinical disease. Weichselbaum initially called the bacterium *Diplococcus intracellularis meningitidis*, reflecting its shape and presence inside phagocytic cells. However, it was subsequently reclassified as *N. meningitidis*. Despite available vaccines against certain strains, *N. meningitidis* continues to be an important cause of septicaemia and meningitis, while the spread of antimicrobial resistant gonococci has emerged as a major public health concern over the past decade, and the bacterium is on the CDC list of urgent threats (http://www.cdc.gov/drugresistance/threat-report-2013/). Thus *Neisseria* have long been recognized as human pathogens, and given the host range of the meningococcus and gonococcus, have been thought of as largely human-specific bacteria.

Abbreviations: NGS, next-generation sequencing; OTU, operational taxonomic unit

In addition to these well-known pathogens, it has become increasingly appreciated that the *Neisseria* genus includes a large number of less well-studied species. *Neisseria* are generally coccoid, Gram-negative organisms that belong to the family Neisseriaceae, which includes other genera of medical importance such as *Kingella* and *Eikenella*. The first isolation of commensal *Neisseria* was *Micrococcus cinereus* (later called *Neisseria cinerea*) in 1906 by von Lingelsheim (von Lingelsheim, 1906), who also described *Neisseria sicca*, *Neisseria flava* and *Neisseria subflava*. Most of these are considered commensals of the human nasopharynx, although some have occasionally caused disease in immune-compromised hosts, or systemic infection, which has resulted following animal bites in susceptible individuals. The commensal *Neisseria lactamica*, in particular, has received significant attention for its potential to protect against *N. meningitidis* either through natural immunity (from carriage) (Evans *et al.*, 2011) or by informing vaccine design. *N. lactamica* is a lactose-fermenting human commensal that is closely related to *N. meningitidis* (Bennett *et al.*, 2005; Hollis *et al.*, 1969). Colonization of the upper respiratory tract by this species starts soon after infants are born. The carriage rate peaks (>20 %) between 1–2 years after birth and thereafter declines with age to a low level (<5 %) in children of 14–17 years old. This is in sharp contrast to the carriage dynamics of *N. meningitidis*, which increases from birth and peaks in 15- to 19-year-olds, and then drops with age (Bennett *et al.*, 2005; Cartwright *et al.*, 1987; Gold *et al.*, 1978). These observations led to the hypothesis that carriage of *N. lactamica* facilitates the development of natural immunity against meningococcus (Gold *et al.*, 1978) and this has been exploited for the design of vaccines

comprising *N. lactamica*-derived antigens, e.g. outer membrane vesicles (Gorringe *et al.*, 2009; Vaughan *et al.*, 2006).

It has become apparent that the *Neisseria* genus is far more abundant, wide-spread and diverse than previously appreciated. For example, the sporadic reports of isolation and characterization of different *Neisseria* species have revealed that this is one of the few bacterial genera that contain members with a spectrum of morphologies, including bacilli and cocci (Fig. 1, Table 1). Further insights into their diversity of habitat and at the genomic level have been provided by advances in nucleotide sequencing, which have unveiled the extent of the human microbial flora, and have provided the whole genome sequence of individual species (Bennett *et al.*, 2012).

Here, we review current knowledge of the members of the *Neisseria* genus, describe the niches that they occupy and their potential to cause disease; we do not discuss human colonization by *N. meningitidis* and *Neisseria gonorrhoeae*, which has been extensively reviewed (Merz & So, 2000; Yazdankhah & Caugant, 2004). It is evident that commensal *Neisseria* species make up a significant proportion of the flora of the human nasal and oropharyngeal flora, and, in sharp contrast to the pathogenic bacteria which are thought to be human-specific (Schook *et al.*, 2011), colonize a wide range of hosts and body sites. We discuss the potential role of *Neisseria* in promoting human health and their exploitation for bioremediation.

Neisseria: a significant component of the human microbiome

In the past, identification of bacteria relied on isolation by culture, followed by biochemical and, more recently, genetic characterization to speciate the isolate. This approach is not feasible when attempting to describe complex communities of microbes in the mammalian gastrointestinal tract or upper airways. Instead, the development of next-generation sequencing (NGS) methods (von Bubnoff, 2008), such as 454 pyrosequencing (Ronaghi *et al.*, 1998), has enabled the use of culture-independent, high-resolution sequencing to assess bacterial diversity and abundance in mixed populations. Total genomic DNA can be sequenced in samples, such as faeces, that are predominantly composed of bacteria. However, contaminating host DNA affects the sensitivity of direct sequencing of nasopharyngeal and throat swabs. Therefore, initial amplification of prokaryotic 16S rRNA gene sequences is often used before sequencing DNA recovered from upper airway samples. Depending on the length and region of 16S rRNA amplified, this does not necessarily provide species-level identification (Claesson *et al.*, 2010). Instead, in some microbiome studies, bacteria are classified into operational taxonomic units (OTUs), which comprise a number of different species that have closely related 16S sequences. Despite these limitations, 16S studies have been effective in characterizing the composition of oral and nasopharyngeal microbiota in humans (Mechergui *et al.*, 2014), and several themes have emerged for commensal *Neisseria* species.

First *Neisseria* species are highly abundant in the human oral cavity. The first study to describe the composition of the human oral microbiome by NGS samples examined saliva from 71 individuals and 98 samples of supragingival plaque from healthy participants (Keijser *et al.*, 2008). More than 19000 species-level phylotypes or OTUs (with a sequence difference cut-off of 6 %) were detected. *Neisseria* was the most abundant genus within Proteobacteria, constituting 8.2 % (425 phylotypes) and 3.9 % (348 phylotypes) of total sequences in saliva and plaque samples, respectively (Keijser *et al.*, 2008). The prevalence of *Neisseria* was further supported by a subsequent study of saliva, mucosal surfaces in the mouth and teeth from three unrelated, healthy individuals, which identified *Neisseria* as part of the healthy 'core microbiome' of the human oral cavity (Zaura *et al.*, 2009).

Secondly, *Neisseria*–human commensalism appears to be conserved across different geographical regions, ethnic groups and lifestyles. The first description of the wide-spread geographical distribution of *Neisseria* came from a study analysing saliva samples from 120 healthy participants (i.e. 10 individuals from each of 12 geographical locations across four continents), in which *Neisseria* was present in the saliva of participants from all locations at high frequency (107 out of 120) (Nasidze *et al.*, 2009). While most oral microbiome studies have been conducted on Caucasians or Asians (Keijser *et al.*, 2008; Ling *et al.*, 2013; Said *et al.*, 2014; Zaura *et al.*, 2009), an interesting investigation focused on isolated communities, with oral swabs taken from six adult Amerindian participants of Guahibo ethnicity living in an isolated rural community of Platanillal, Amazonas State, Venezuela (Contreras *et al.*, 2010). Although the genera detected in the Amerindians were substantially less diverse than in non-Amerindians, *Neisseria* was still the predominant genus among the *Proteobacteria*, which itself was one of the four most abundant phyla along with *Firmicutes*, *Bacteroidetes* and *Actinobacteria* (Contreras *et al.*, 2010).

Third, *Neisseria* spp. appears to be an early colonizer of human oral and nasopharyngeal cavities. A study from 1965, using a culture-dependent methods, analysed oral swabs from the upper and lower dental ridges from infants at different ages after birth (McCarthy *et al.*, 1965). *Neisseria* was found in 4 of 51 infants within the first week of life and its incidence increased with age (i.e. 30 carriers out of 44 at 101 days, and 29 out of 29 at days 248 and 365) (McCarthy *et al.*, 1965). A more recent study using NGS also observed the same trend; saliva samples were collected from five oedentulous infants aged 3–6 months and their mothers or primary carers. More than 200 genera were identified in infants, with *Neisseria* being one of the predominant genera (Cephas *et al.*, 2011). In addition to the oral cavity, the composition of the nasopharyngeal microbiome has been investigated by barcoding

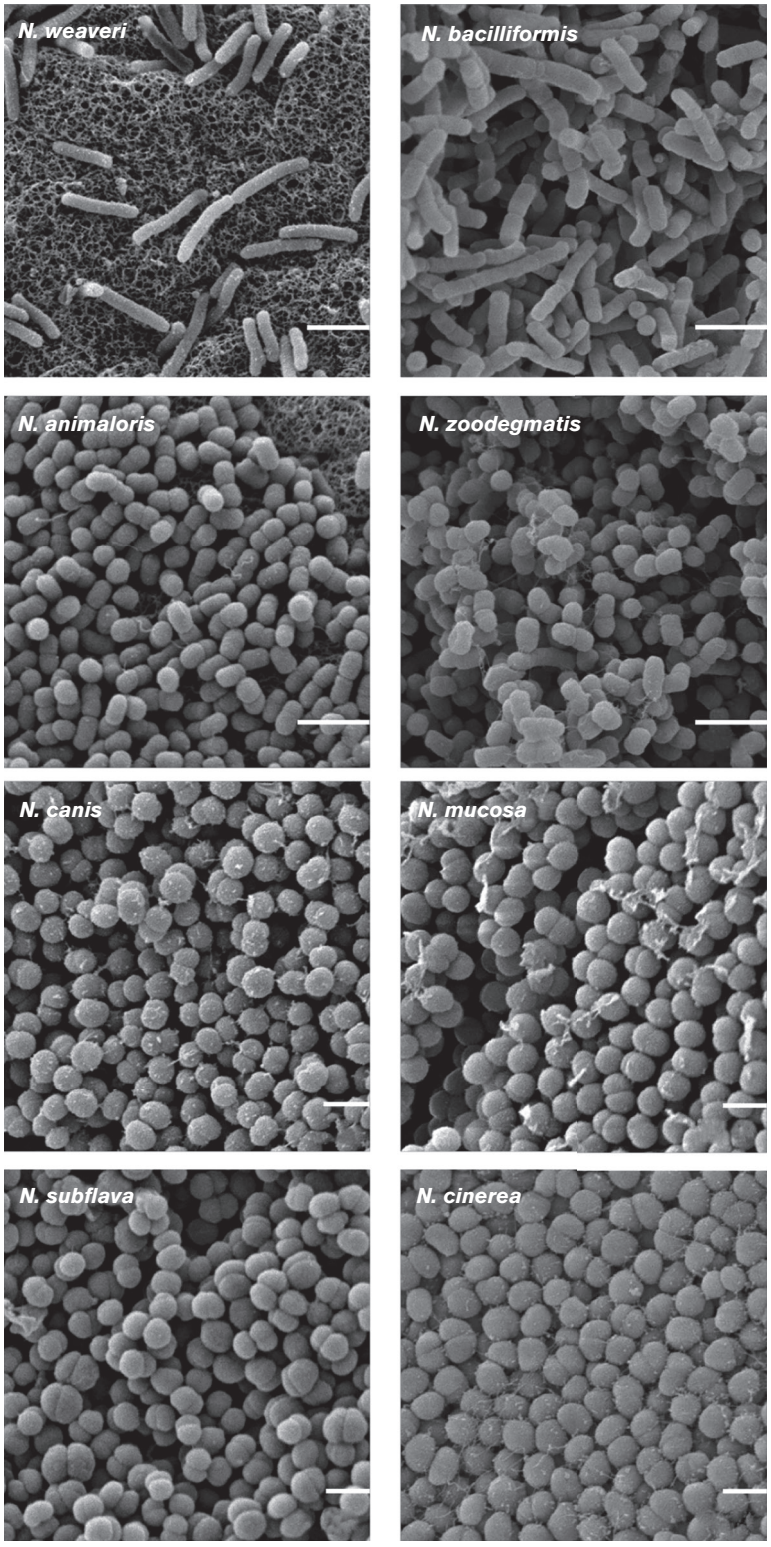

Fig. 1. *Neisseria* species display a spectrum of morphologies. Scanning electron micrographs of different species of *Neisseria*. *N. weaveri* (CCUG 4007^T) and *N. bacilliformis* (CCUG 50611) are rod-shaped, *N. animaloris* (NCTC 12228^T) and *N. zoodegmatis* (NCTC 12230^T) are coccobacilli and *N. canis* (CCUG 56775^T), *N. mucosa* (CCUG 805), *N. subflava* (CCUG 801) and *N. cinerea* (CCUG 346^T) are diplococci. Bacteria were grown overnight on BHI agar plates. Blocks of agar with colonies were excised and prepared for SEM using a protocol adapted from Bozzola (2007), then imaged on a JEOL-6390 scanning electron microscope. Bars, 2 μm (upper four panels), 1 μm (lower four panels).

pyrosequencing in 96 healthy children of 18 months of age (Bogaert *et al.*, 2011). In contrast to *Firmicutes* in the oral cavity, *Proteobacteria* was the most predominant phylum in the nasopharynx and although *Neisseria* is still abundant, it was not the most prevalent genus within *Proteobacteria*. However, *N. meningitidis* was found in 62 out of 96 participants (Bogaert *et al.*, 2011).

Finally, *Neisseria* colonization of the human oral cavity has been detected in a recent metagenomic study characterizing the microbiota associated with ancient dental calculus from four adults with periodontal disease from the medieval monastic site at Dalheim, Germany; four *Neisseria* species were identified, including *N. meningitidis*, *N. gonorrhoeae*, *N. sicca* and *N. subflava* (Warinner *et al.*, 2014).

Identification of *Neisseria* species in non-human mammalian hosts

While commensal *Neisseria* species only colonize the oral and nasopharyngeal cavities of humans, they can be found in a far wider range of body sites in animals (Table 2). The habitats of commensal *Neisseria* in mammals are similar to those in humans, probably due to the shared anatomical and physiological features. For example in non-human primates, the oral and nasopharyngeal microbiome has been most extensively studied in the rhesus macaque (*Macaca mulatta*) given its potential as an animal model for human-specific pathogens such as *N. meningitidis* (Weyand *et al.*, 2013). Although *Neisseria* species were identified in all rhesus macaque studies, their prevalence appeared to be lower than that in humans. In an early study, *Neisseria macacae* was found as a new species of the oropharynx of the rhesus macaque (Vedros *et al.*, 1983). Subsequently, nasal and pharyngeal swabs were taken from 55 healthy rhesus macaques and *Neisseria* species were identified in the nose and pharynx of one and seven macaques, respectively (Bowers *et al.*, 2002). Two isolates were identified as *N. sicca*, with *N. meningitidis* not detected (Bowers *et al.*, 2002). Another study of 24 healthy male rhesus macaques identified *N. cinerea* and *N. flava* from oropharyngeal samples of one and two macaques, respectively, with no *Neisseria* detected in rectal samples (Carrier *et al.*, 2009). Apart from the rhesus macaque, a few other non-human primates have been studied. Using a culture-dependent approach, analysis of dental plaque showed that sooty mangabeys, patas monkeys, aotus monkeys and ruffed lemurs at London Zoo all carry both polysaccharide-producing and non-polysaccharide-producing *Neisseria* species (Dent & Marsh, 1981). Similar results were obtained in a recent survey of chimps at Ngamba island sanctuary in Uganda; culture and 16S rRNA analyses detected *Neisseria* species, including *N. meningitidis* in oral and nasal samples (Mugisha *et al.*, 2014).

Dogs and cats have been the focus of many oral microbiome studies for two main reasons: oral bacterial infections can cause morbidity in these important domestic pets (Verhaert & Van Wetter, 2004), while dog and cat bites are a public health concern (Abrahamian & Goldstein, 2011; Umeda *et al.*, 2014). Commensalism of *Neisseria* in dogs has long been recognized. For example, in the 1960s, *N. sicca* and *Neisseria flavescens* were identified in the noses and throats of beagles, but not in the rectum (Clapper & Meade, 1963). More recently, *N. flavescens*, *Neisseria N. sicca* and CDC Group EF-4 (Cent for Disease Control for Eugonic Fermenter 4) were detected in nasal and oral samples, while CDC Group M-5 were only identified in oral fluids (Bailie *et al.*, 1978). CDC Group EF-4 is divided into two biovars, EF-4a and EF-4b (based on their ability to synthesize arginine dihydrolase) and they were specifically studied; 92 % of 49 dogs carried EF-4 strains which were mostly EF-4b isolates (Ganière *et al.*, 1995). All EF-4 and CDC Group M-5 strains have since been classified into the *Neisseria* genus based on 16S rRNA sequences and redesignated *Neisseria animaloris* (EF-4a), *Neisseria zoodegmatis* (EF-4b) and *Neisseria weaveri* (M-5) (Andersen *et al.*, 1993; Vandamme *et al.*, 2006). Furthermore 16S rRNA sequencing has been used to investigate the oral microbiota. The saliva and dental plaque of nine healthy dogs were sampled, and *Neisseria canis* and *N. weaveri* were identified at species level (Elliott *et al.*, 2005). The non-cultivable canine oral flora has also been characterized by metagenomic study using NGS. Oral samples were collected from six healthy dogs, and 23 OTUs with 97 % similarity were identified within the

Table 1. Different morphology of *Neisseria* species

Species	Morphology	Reference
N. weaveri	Bacillus	Andersen *et al.* (1993)
N. elongata	Bacillus	Bovre & Holten (1970)
N. bacilliformis	Bacillus	Han *et al.* (2006)
N. shayeganii	Bacillus	Wolfgang *et al.* (2011)
N. animaloris	Coccobacillus	Ganière *et al.* (1995)
N. zoodegmatis	Coccobacillus	Ganière *et al.* (1995)
N. tadorna	Diplococcus	Wang (2011)
N. canis	Diplococcus	Berger (1962)
N. denitrificans	Diplococcus	Berger (1962)
N. animalis	Diplococcus	Berger (1960)
N. dentiae	Diplococcus	Sneath & Barrett (1996)
N. iguanae	Diplococcus	Plowman *et al.* (1987)
N. wadsworthii	Diplococcus	Wolfgang *et al.* (2011)
N. macacae	Diplococcus	Vedros *et al.* (1983)
N. oralis	Diplococcus	Wolfgang *et al.* (2013)
N. mucosa	Diplococcus	Veron *et al.* (1959)
N. sicca	Diplococcus	Shaw (1932)
N. flavescens	Diplococcus	Branham (1930)
N. subflava	Diplococcus	Benson *et al.* (1928)
N. lactamica	Diplococcus	Hollis *et al.* (1969)
N. polysaccharea	Diplococcus	Riou & Guibourdenche (1987)
N. cinerea	Diplococcus	Knapp *et al.* (1984)
N. skkuensis	Coccus	Park *et al.* (2012)

Table 2. *Neisseria* species in non-human hosts

*PP, polysaccharide producing; NPP, non-polysaccharide producing. In the report of Dent & Marsh (1981), further speciation of the *Neisseria* isolated was not described. Therefore the PP/NPP criterion is shown in this table for classification.

Animal host	Isolation site	Species*	Method	Reference
Dog	Nose	*N. flavescens*	Culture-dependent	Clapper & Meade
	Throat	*N. flavescens*		
		N. sicca		
	Nasal and oral cavity	CDC group EF-4	Culture-dependent	Bailie *et al.* (1978)
		CDC group M-5		
		N. mucosa		
		N. flavescens		
		N. sicca		
	Saliva and dental plaque	*N. canis*	Culture-dependent	Elliott *et al.* (2005)
		N. weaveri		
	Oral cavity	*Neisseria*	Culture-independent	Sturgeon *et al.* (2013)
	Dental plaque	*N. shayeganii*	Culture-independent	Holcombe *et al.* (2014)
		N. weaveri		
		N. zoodegmatis		
	Mandibular abscess	*N. canis*	Culture-dependent	Cantas *et al.* (2011)
		N. weaveri		
	Lung	CDC group EF-4	Culture-dependent	McParland *et al.* (1982)
Badger	Lung, spleen, and liver	CDC group EF-4	Culture-dependent	Corboz *et al.* (1993)
Cat	Lung	CDC group EF-4	Culture-dependent	Corboz *et al.* (1993)
	Oral cavity	*Neisseria*	Culture-dependent and -independent	Dolieslager *et al.* (2011)
	Oral cavity	*Neisseria*	Culture-independent	Sturgeon *et al.* (2014)
Chinese leopard cat	Lung	CDC group EF-4	Culture-dependent	Perry & Schlingman (1988)
African lion	Lung	CDC group EF-4	Culture-dependent	Fenwick *et al.* (1983)
Tiger	Lung	CDC group EF-4	Culture-dependent	Lloyd & Allen (1980)
	Dental plaque	*Neisseria* (NPP)	Culture-dependent	Dent & Marsh (1981)
Blotched genet	Dental plaque	*Neisseria* (NPP)	Culture-dependent	Dent & Marsh (1981)
Giraffe				
Sooty mangabey		*Neisseria* (PP, NPP)		
Patas monkey				
Aotus monkey				
Ruffed lemur				
Rhesus macaque	Oropharynx	*N. macacae*	Culture-dependent	Vedros *et al.* (1983)
	Nasal and pharyngeal cavities	*Neisseria* including *N. sicca*	Culture-dependent	Bowers *et al.* (2002)
	Oropharynx	*N. cinerea*	Culture-dependent	Carrier *et al.* (2009)
		N. flava		
Chimpanzee	Oral cavity and nasopharynx	*Neisseria* including *N. meningitidis*	Culture-dependent	Mugisha *et al.* (2014)
Tree shrew	Oral cavity	*N. mucosa*	Culture-dependent	Li *et al.* (2014)

Table 2. cont.

Animal host	Isolation site	Species*	Method	Reference
Horse	Nasal cavity	*Neisseria*	Culture-dependent	Jannatabadi *et al.* (2008)
Goat	Skin	*Neisseria*	Culture-dependent	Kayalvizhi *et al.* (2008)
Sheep				
Cow	Oral cavity	*N. dentiae*	Culture-dependent	Sneath & Barrett (1996)
Guinea pig	Oral cavity	*N. animalis*	Culture-dependent	Berger (1960)
	Throat	*N. denitrificans*	Culture-dependent	Berger (1962)
Quokka (*Setonix brachyurus*)	Marsupium	*Neisseria*	Culture-dependent	Yadav *et al.* (1972)
Californian sea lion (*Zalophus californianus*)	Nasal cavity	*Neisseria* including *N. flavescens* and *N. mucosa*	Culture-dependent	Hernández-Castro *et al.* (2005)
Dolphin (*Lagenorhynchus obliguidens*)	Blowhole	*N. mucosa* var. *heidelbergensis*	Culture-dependent	Vedros *et al.* (1973)
Dolphin (*Delphinus bairdi*)	Blowhole, mouth and throat	*N. mucosa* var. *heidelbergensis*		
Rhinocerus iguana (*Cyclura cornuta*) Common iguana (*Iguana iguana*)	Oral cavity, liver, and tail abscesses	*N. iguanae*	Culture-dependent	Plowman *et al.* (1987)
American black vulture (*Coragyps atratus*)	Tongue	*N. sicca*	Culture-dependent	De Carvalho *et al.* (2003)
Duck (*Anas platyrynchos* or its hybrid with *Anas superciliosa*)	Faeces immediately after defecation	*N. mucosa and* two unknown *Neisseria* species	Culture-dependent	Murphy *et al.* (2005)
Northern bobwhite (*Colinus virginianus*)	Caecum	*N. flavescens*	Culture-dependent	Su *et al.* (2014)
	Cloaca	*N. flavescens* *N. sicca* *N. meningitidis*		
Gaoyou sheldrake	Liver	*N. tardona*	Culture-dependent	Wang (2011)
Pekin duck	Liver	*Neisseria* sp. AH-N10	Culture-dependent	Wang *et al.* (2014)
Macaroni and little penguins	Faeces from rectal swabs	*Neisseriacae*	Culture-independent	Dewar *et al.* (2013)
Mosquito (*Anopheles gambiae*)	Midgut	*Neisseria*	Culture-independent	Boissière *et al.* (2012)
Mosquito (*Anopheles culicifacies*)	Salivary gland	*Neisseria*	Culture-independent	Sharma *et al.* (2014)
Mosquito (*Aedes albopictus*)	Whole body homogenate	*Neisseria*	Culture-dependent	Valiente Moro *et al.* (2013)
Fly (12 species)	Body surface	*Neisseria*	Culture-dependent	Förster *et al.* (2007)
House fly (*Musca domestica*)	Pupa	*Neisseria*	Culture-independent	Wei *et al.* (2013)
Cattle tick (*Rhipicephalus microplus*)	Adult male, egg	*Neisseria*	Culture-independent	Andreotti *et al.* (2011)
African honeybee (*Apis mellifera scutellata*)	Abdomen	A species most closely related to *N. meningitidis* and *S. muelleri*	Culture-independent	Jeyaprakash *et al.* (2003)
Common woodlouse (*Porcellio scaber*)	Hindgut	*N. perflava* *N. mucosa* *N. flavescens*	Culture-independent	Kostanjšek *et al.* (2002)

Neisseria genus; two of these OTUs belong to the core microbiome (i.e. present in all six dogs) (Sturgeon *et al.*, 2013).

There are fewer studies characterizing the composition of the healthy feline microbiome. Dolieslager *et al.* (2011) investigated the oral microbiota of three healthy cats and five cats with feline chronic gingivostomatitis, and *Neisseria* was only found in healthy cats. A more comprehensive NGS-based approach has characterized the oral microbiota of 11 healthy cats, and once more, *Neisseria* was a predominant taxon and part of the core microbiome (Sturgeon *et al.*, 2014).

Neisseria spp. have also been identified in the nasal and oral cavities of several herbivorous mammals (Table 2), including the novel species *Neisseria animalis*, *Neisseria denitrificans* from guinea pigs (Berger, 1960; 1962) and *Neisseria dentiae* from domestic cows (Sneath & Barrett, 1996). Interestingly, three strains of *Neisseria* were identified from skin samples of sheep and goats (Kayalvizhi *et al.*, 2008), which is in contrast to humans, where *Neisseria* is not part of the skin microbiota.

Neisseria has been found in marsupials (Table 2). The microflora of the alimentary tract of the pouch-young and the pouch of adult Quokka, a macropod, was characterized (Yadav *et al.*, 1972). *Neisseria* was isolated from one adult without pouch-young and, similar to other mammals, no alimentary tract-associated *Neisseria* was identified (Yadav *et al.*, 1972).

Neisseria–mammal commensalism even extends to marine animals (Table 2). In 1973, the first investigations were made into the presence of *Neisseria* in two dolphin species, *Lagenorynchus obliguidens* and *Delphinus bairdi*. Samples were taken from extensive sites and one *Neisseria* strain highly similar to *N. mucosa* var. *heidelbergensis* was isolated from the blowholes of two out of 35 *L. obliguidens*, and from the throat, mouth and blowhole of *D. bairdi* (Vedros *et al.*, 1973). Consistent with this, *Neisseria* species including *N. mucosa* and *N. flavescens* were isolated from the nasal cavity of healthy Californian sea lion pups in the Gulf of California (Hernández-Castro *et al.*, 2005). The colonization of the nasal cavity and blowhole (an anatomical homologue of the nostril) of marine mammals further supports that *Neisseria* spp. are highly adapted to this niche.

Neisseria is widespread in non-mammalian hosts

In contrast to mammalian *Neisseria*, avian *Neisseria* species tend to colonize the digestive tract, suggesting faecal–oral transmission (Table 2). For instance, *N. mucosa* and two unknown *Neisseria* species have been found in faeces from two duck species, the mallard duck and its hybrid with the grey duck (Murphy *et al.*, 2005). Of note, chickens, another economically important fowl, have not been reported to carry *Neisseria* to date in spite of a large number of studies. To characterize variations of gastrointestinal microbiota in four species of penguin, faecal samples were taken from the king, gentoo, macaroni and little penguins and subject to NGS analysis. Sequences from the *Neisseriacae* family were only dominant in macaroni and little penguins, suggesting host specificity. Unfortunately the resolution of the analysis did not allow genus level identification (Dewar *et al.*, 2013). However, subsequently *Neisseriacae* was found in both the king and little penguins dependent on the moulting stage, indicating the abundance of *Neisseriacae* is influenced by host physiology (Dewar *et al.*, 2014).

In addition to waterfowls and penguins, *Neisseria* has been identified in ground-dwelling birds such as northern bobwhites (Su *et al.*, 2014). *N. flavescens* was isolated from the caecumwhile *N. flavescens*, *N. Sicca* and *N. meningitidis* (based on 16S rRNA sequencing of individual colonies) from the cloaca in bobwhites. However, by culture, *N. sicca* was only identified in the tongue sample of one of six American black vultures, and not from any lower intestinal site (De Carvalho *et al.*, 2003).

Insects have been the focus of research for centuries as vectors of disease and because of their economic importance (e.g. honey bees and silkworms). There has been growing interest in characterizing the insect-associated microbiome as it profoundly influences the physiology (Dillon & Dillon, 2004; Ryu *et al.*, 2008) and the vector competency of the insect host (Dong *et al.*, 2009; Xi *et al.*, 2008). Progress in this field has been accelerated by the application of culture-independent methods, especially NGS.

Neisseria was first shown to be associated with insects in 2007 in fly species associated with humans; *Neisseria* species were identified in four out of 56 flies (Förster *et al.*, 2007). Later, Wei *et al.* (2013) characterized the bacterial communities associated with houseflies at different developmental stages, and found *Neisseria* species in pupae but not in maggots or adult flies. In addition, flies have been implicated in epidemics of gonococcal conjunctivitis in Aboriginal populations in Australia (Brennan *et al.*, 1989; Matters *et al.*, 1998; Merianos *et al.*, 1995). Interestingly, one outbreak was caused by a single *N. gonorrhoeae* strain that was distinct from all genital isolates. More strikingly, this strain seemed to begin to infect patients in a single district, then spread hundreds of kilometres to the east and south through arid areas (Mak *et al.*, 2001), which the authors suggest was unlikely to be solely mediated by human activity. Moreover, there was heavy rainfall one month before the first case, and an extremely high fly population during the first three months of the epidemic, suggesting flies might act as a vector (Matters *et al.*, 1998). In fact, the Australian bushfly was proposed to play such a role in the transmission of gonoccocal conjunctivitis years before this outbreak (Weinstein, 1991). Despite this, the gonococcus has not yet been identified from flies.

Neisseria species have also been identified in other disease-transmitting insect vectors, with their distribution displaying gender and tissue specificity. Comparison of lab reared and field-collected *Anopheles gambiae* (an important vector

of malaria) revealed that the midgut flora of lab-reared mosquitoes was dominated by *Flavobacteria* (>96 %), while the flora of field-collected mosquitoes was dominated by *Proteobacteria* and displayed greater diversity. Specifically, *Neisseria* was identified in 16 out of 28 field-collected mosquitoes (Boissière *et al.*, 2012). Additionally, NGS of the flora of the dominant malaria vector in India, *Anopheles culicifacies*, demonstrated that salivary gland microbiota (76 genera) was more diverse than the midgut (46 genera), with *Neisseria* only found in salivary glands (Sharma *et al.*, 2014). *Neisseria* has also been found in *Aedes albopictus*, a vector of Yellow fever, Dengue fever, and Chikungunya fever viruses, but only isolated from male mosquitoes (Valiente Moro *et al.*, 2013).

In contrast to mosquitoes, which are vectors for eukaryotic parasites and viruses, ticks are more associated with the transmission of bacterial pathogens, such as *Borrelia*, *Rickettsia*, *Francisella* and *Coxiella*. To date, *Neisseria* has only been identified in adult male and egg samples from lab-reared cattle ticks (Andreotti *et al.*, 2011). A new species, most closely related to *N. meningitidis* and *Simonsiella muelleri*, was identified in Western honey bees (Jeyaprakash *et al.*, 2003), while *Neisseria perflava*, *N. mucosa* and *N. flavescens* have been found in the hindgut of the common woodlouse, *Porcellio scaber* (Kostanjšek *et al.*, 2002).

Free-living *Neisseria*

There have been sporadic reports of *Neisseria* species in the environment with no obvious association with a host (Table 3). Environmental *Neisseria* was first reported in Japan, when *N. sicca* was recovered from soil and found to assimilate cellulose acetate, an organic ester which is widely used in industry (Sakai *et al.*, 1996). Later, *Neisseria* was isolated from contaminated water, soil and sediment in Mexico and shown to be able to degrade dichlorodiphenyltrichloroethane (Carrillo-Pérez *et al.*, 2004). The ability of *Neisseria* to degrade organic pollutants has been confirmed in different contexts. Borin *et al.* (2006) reported *Neisseria* as the dominant genus in the packing material of a biofilter used to remove benzene, and showed that two *Neisseria* strains can grow using benzene as the sole carbon source. Furthermore, *Neisseria* species SY22 was isolated from crude oil-contaminated soil from four oil wells in China and was found to display good bioremediation capacity against crude oil, naphthalene and xylene (Xu *et al.*, 2014).

Neisseria have been found in sites closely associated with humans, and are, for example, a component of the microbiota of showerhead biofilms as determined by DNA analysis (Feazel *et al.*, 2009) and mattress dust (Ege *et al.*, 2012). Of note, there was a significant inverse correlation between the onset of hay fever with the detection of *Neisseria* in mattress dust, suggesting that exposure to *Neisseria* might confer a degree of protection to children (Ege *et al.*, 2012). Potential environmental reservoirs and transmission have been invoked to explain the seasonal outbreaks of meningococcal disease in sub-Saharan Africa during the dry season; regional wind speeds and surface dust concentrations are good predictors of the incidence of meningitis (Pérez García-Pando *et al.*, 2014), which further links meningitis epidemics in Africa with environmental risk factors (Martiny & Chiapello, 2013; Molesworth *et al.*, 2003; Sultan *et al.*, 2005). Further circumstantial evidence comes from studies of the persistence of *N. meningitidis* on environmental surfaces, which indicate that the bacterium can survive desiccation from hours to days (Downie, 1940; Swain & Martin, 2007; Tzeng *et al.*, 2014; Walther & Ewald, 2004).

Disease associated with commensal *Neisseria*

Although less virulent than *N. meningitidis* and *N. gonorrhoeae*, commensal *Neisseria* can be opportunistic pathogens in humans (Table 4). Notably, although *Neisseria polysaccharea* is the most evolutionarily related species to *N. meningitidis* and *N. gonorrhoeae* (Bennett *et al.*, 2013; Bennett *et al.*, 2014), there are far fewer case reports for disease caused by this species compared with *N. lactamica* and *N. cinerea*.

Table 3. Summary of reported free-living *Neisseria* species

Isolation site	Species	Method	Reference
Soil	*N. sicca*	Culture-dependent	Sakai *et al.* (1996)
Contaminated water, soil and sediment	*Neisseria*	Culture-dependent	Carrillo-Pérez *et al.* (2004)
Water and sediment	*N. mucosa* *N. sicca*	Culture-dependent	Thavasi *et al.* (2007)
Oil-polluted soil	*Neisseria*	Culture-dependent	Xu *et al.* (2014)
Biofilter packing material	*Neisseria*	Culture-dependent and -independent	Borin *et al.* (2006)
Showerhead biofilms	*Neisseria*	Culture-independent	Feazel *et al.* (2009)
Mattress dust	*N. meningitidis* *N. mucosa* *N. subflava*	Culture-independent	Ege *et al.* (2012)
House dust	*Neisseria*	Culture-independent	Konya *et al.* (2014)

Table 4. Summary of infections attributed to commensal *Neisseria* species

Species	Case report(s)	Reference
N. weaveri	**Septicaemia:** 69-year-old male with type 2 diabetes, after dog bite	Carlson *et al.* (1997)
	Lower respiratory tract infection: 60-year-old male with 15-year bronchiectasis	Panagea *et al.* (2002)
	Peritonitis: 35-year-old male after 3 months continuous ambulatory peritoneal dialysis due to end-stage renal disease	Kocyigit *et al.* (2010)
N. canis	**Fever:** 36-year-old healthy female after a cat-bite, mixed culture with *P. multocida*	Guibourdenche *et al.* (1989)
	Purulent wound and cellulitis: 50-year-old healthy male after treading on a dog bone	Safton *et al.* (1999)
	Long-term respiratory tract infection: 66-year-old male poodle owner with chronic obstructive pulmonary disease complicated by bronchiectasis	Allison & Clarridge (2005)
N. animaloris	**Infection following animal bite:** multiple cases	Holmes *et al.* (1990)
	Chronic otitis media: 36-year-old male after ears licked by dog	Roebuck & Morris (1999)
N. zoodegmatis	**Infection following animal bite:** multiple cases	Holmes *et al.* (1990)
	Skin ulceration: 27-year-old male former drug addict with AIDS	Grob *et al.* (1989)
N. bacilliformis	**Subacute endocarditis:** 47-year-old male with heart murmur and peripheral facial nerve palsy	Masliah-Planchon *et al.* (2009)
	Endocarditis: 60-year-old male with hypertension	Abandeh *et al.* (2012)
N. elongata	**Osteomyelitis:** 49-year-old healthy male 10 months after incisor tooth abscess de-roof	Garner & Briant (1986)
	Endocarditis: 54-year-old healthy male 4 months after a dental treatment	Haddow *et al.* (2003)
	Endocarditis and septicaemia: 30-year-old male with known hypertrophic obstructive cardiomyopathy, treated with verapamil	Hofstad *et al.* (1998)
N. subflava	**Meningitis and septicaemia:** Five cases in children	Lewin & Hughes (1966)
	Bacteraemia: 61-year-old female, 12 years after a renal transplant with low blood polymorphonuclear leukocytes due to steroid treatment	Ramos *et al.* (1998)
	Endocarditis: 49-year-old woman, 1 year after prosthetic mitral valve implant	Molina *et al.* (2000)
	Co-infection with *H. pylori* to trigger lymph follicle formation in stomach: multiple cases	Nakamura *et al.* (2006)
N. flavescens	**Endocarditis:** 82-year-old female with type 2 diabetes, aortic sclerosis and hypertension	Sinave & Ratzan (1987)
	Septicaemia: 20-year-old healthy female, 7 days after dental surgery	Wertlake & Williams (1968)
	Necrotizing pneumonia and empyema: 58-year-old male with type 2 diabetes, hypertension and 40-year smoking history	Huang *et al.* (2014)
N. mucosa	**Meningitis:** 33-year-old female, after ventriculoperitoneal shunt implant	Stotka *et al.* (1991)
	Endocarditis: 21 cases	Pilmis *et al.* (2014)
	Septicaemia: 71-year-old male, 1 year after mitral and aortic valve replacement	Locy (1995)
	Visceral botryomycosis: 20-year-old male with chronic granulomatous disease	Washburn *et al.* (1985)
N. sicca	**Endocarditis:** 17 cases mostly associated with mitral valve replacement	Sommerstein *et al.* (2013)
	Meningitis: 44-year-old female following intracranial haemorrhage and ventriculostomy tube placement	Carter *et al.* (2007)
	Conjunctivitis: 79-year-old female with no history of trauma or surgery	Eser *et al.* (2014)
N. skkuensis	**Fever and foot ulcer:** 50-year-old male with type 2 diabetes, suffering from complications	Lee *et al.* (2010)
	Prosthetic valve endocarditis: 41-year-old male with liver cirrhosis, chronic kidney disease, 1 year after a mechanical mitral valve replacement due to endocarditis caused by MRSA	Park *et al.* (2012)
N. cinerea	**Peritonitis:** 38-year-old male with type 2 diabetes, 2 years after end-stage renal disease and CAPD	Taegtmeyer *et al.* (2006)
	Neonatal conjunctivitis: new born, from mother during birth	Bourbeau *et al.* (1990)
	Bacteraemia: 47-year-old male, underlying ethanol abuse and polymicrobial sepsis	Southern & Kutscher (1987)

Table 4. cont.

Species	Case report(s)	Reference
	Proctitis: 8-year-old male	Dossett *et al.* (1985)
	Nosocomial pneumonia: 25-year-old male with AIDS	Boyce *et al.* (1985)
	Tricuspid valve endocarditis: 34-year-old male, IV drug user	Benes *et al.* (2003)
	Meningitis and septicaemia: 17-year-old male, facial trauma, alveolodental luxation. Likely via microfissure as RBC in CSF	Kirchgesner *et al.* (1995)
N. lactamica	**Arthritis and septicaemia:** 60-year-old male, immune suppressed by myeloma and corticosteroids	Everts *et al.* (2010)
	Cavitary lung disease: 64-year-old male, 2 years after a cadaver kidney allograft	Zavascki *et al.* (2006)
	Bacteraemic pneumonia: 42-year-old male with 4 year history of HBV-associated Child C liver cirrhosis and 20-year smoking history	Wang *et al.* (2006)

Some *Neisseria* species have been reported to be bona fide animal pathogens (Table 2). In mammals, *N. animaloris* (EF-4a) and *N. zoodegmatis* (EF-4b) cause disease in animals within the Felidae family, including more than ten cases of disease in cats (Baral *et al.*, 2007; Corboz *et al.*, 1993; McParland *et al.*, 1982), two Chinese leopards, a lion and a tiger cub (Fenwick *et al.*, 1983; Lloyd & Allen, 1980; Perry & Schlingman, 1988). In addition to those, cases caused by group EF-4 bacteria have also been reported in dogs and badgers (Cantas *et al.*, 2011; Corboz *et al.*, 1993; McParland *et al.*, 1982). The mechanisms underlying the pathogenesis of infection caused group EF-4 bacteria are not well understood. While the clinical symptoms appeared acute, necropsy and histological data often reflect a chronic process (Baral *et al.*, 2007). It has been proposed that chronic infection circumvents host immunity, leading to periodic asymptomatic bacteraemia with haematogenous dissemination to locations that favour survival and growth, such as lungs in cats, which then triggered the acute terminal exacerbation (Baral *et al.*, 2007; Fenwick *et al.*, 1983).

In 1984 and 1985, at the National Zoological Park in Washington, DC, an outbreak occurred in iguanid lizards. Initially, a rhinocerous iguana died from septicaemia. Later, four common iguanas were found to have multiple chronic tail abscesses. A single species of *Neisseria* was isolated from the liver of the rhinocerous iguana, the tail abscesses and from the mouths of healthy common and rhinocerus iguanas, suggesting transmission via biting (Plowman *et al.*, 1987). Later, this organism was proposed to be a new species, *Neisseria iguanae* (Barrett *et al.*, 1994). Besides in mammals and reptiles, a new *Neisseria* species, *Neisseria tardona*, was isolated from the liver of the gaoyou sheldrake, a waterfowl in China (Wang, 2011). In 2012, an epidemic of a *Neisseria* species caused high mortality in Pekin ducks in Anhui, China, and was characterized by conjunctivitis, diarrhoea and decreased egg production; necropsy revealed symptoms of systemic disease (Wang *et al.*, 2014).

Commensal *Neisseria* as biomarkers of human disease

Although in most cases *Neisseria* species are benign commensals in the oral and nasopharyngeal cavities of their human host, their presence and abundance have been correlated with the onset and progression of many diseases.

Given their abundance in the oral cavity, several studies have evaluated the role of *Neisseria* species in dental caries. A study of children between three and 18 years of age revealed that *Neisseria* is highly prevalent (97 % of 74 saliva samples) and a single probe for *N. flavescens* was significantly associated with a caries-free oral status (Crielaard *et al.*, 2011). In contrast, in two NGS-based studies targeting younger children in China, *Neisseria* was found to be a predominant genus, although its abundance was not related to dental caries (Ling *et al.*, 2010; Xu *et al.*, 2014).

Neisseria species have been identified from sputum samples of patients with lower respiratory tract infection (Zhou *et al.*, 2010), although this does not provide evidence for an aetiological role in disease. Moreover, to characterize the microbial community in individuals with cystic fibrosis (CF), sputum samples were analysed from 22 clinically stable patients and 13 patients undergoing acute exacerbation (Filkins *et al.*, 2012). Of note, microbiome diversity correlates positively with stable CF, with *Neisseria* decreasing in patients during acute exacerbation (Filkins *et al.*, 2012).

The abundance of oral *Neisseria* species also appears to be associated with human lipid metabolism. To characterize the roles played by oral and gut microbiota in the development of atherosclerosis, Koren *et al.* (2011) analysed the oral, gut and atherosclerotic plaque microbiota from patients and healthy controls. Although *Neisseria* was not identified in atherosclerotic plaques, its oral abundance is negatively correlated with levels of high-density lipoprotein and apolipoprotein AI, which are protective against atherosclerosis. Moreover, *N. mucosa* has been found to be present in sixfold higher amounts among obese participants

compared with normal weight indviduals (Zeigler *et al.*, 2012).

Inflammatory bowel disease (IBD) has oral manifestations such as ulcers and dry mouth, suggesting a role for the oral microbiota in the disease (Curtis *et al.*, 2011; Veloso, 2011). It was shown that there is a significant increase in *Bacteroidetes* in the salivary microbiota of IBD patients with a concurrent reduction in *Proteobacteria*, mainly due to reduced carriage of *Neisseria*. Specifically, the abundance of *N. mucosa* is twofold less in IBD patients compared with healthy controls (Said *et al.*, 2014).

A few studies have reported a positive correlation between oral and pancreatic cancer (Hujoel *et al.*, 2003; Michaud *et al.*, 2007; Stolzenberg-Solomon *et al.*, 2003). To further characterize the association between oral microbiota and pancreatic diseases, Farrell *et al.* (2012) detected a significant difference in the salivary microbiota of patients with pancreatic cancer and healthy controls, using human oral microbe identification microarrays and qPCR. More specifically, *N. elongata*, along with *Streptococcus mitis*, was shown to be significantly less abundant in patients with pancreatic cancer than healthy controls.

DISCUSSION

Neisseria are most notorious for disease caused by the closely related human pathogens, *N. meningitidis* and *N. gonorrhoeae*. *Neisseria* is a highly abundant component of the human oropharyngeal microbiome and a major challenge is to understand whether this commensal population contributes to human health, and how it impacts colonization and disease caused by the meningococcus. There is remarkable, yet largely unappreciated, diversity in *Neisseria* at the genetic, morphological and phenotypic level. The genus has clearly been successful in finding niches at a number of distinct body sites in a broad range of hosts. The main non-human habitat for *Neisseria* is primarily in the upper airways of other animals, yet is also found in the lower intestinal tract, particularly in avian hosts. In rare instances, *N. meningitidis* has been isolated from non-human hosts, although these reports must be confirmed to change perceptions of the host restriction of this important human pathogen. The *Neisseria* genus also contains both coccoid and rod-shaped species, and thus provides an ideal model system for comparative studies to dissect the molecular mechanisms of bacterial morphogenesis. Currently this remains unexplored, but elucidating the mechanisms which govern bacterial cell shape has important implications for understanding bacterial growth and division (Jiang *et al.*, 2015) and may provide us with novel targets for antimicrobials. Furthermore, analysis of the basis of host cell adhesion and immune evasion in a commensal with a broad host range could reveal why the pathogenic species are only found in humans. Similar studies have provided insights into the biology of *Salmonella typhi* (Spanò & Galán, 2012).

Finally, environmental *Neisseria* may have an important role in bioremediation and for biotechnology, given the ease with which other members of the genus can be genetically manipulated, and their degradative capacity. Whole genome sequencing should pave the way for defining the genes responsible for key biosynthetic and metabolic pathways, and the generation of designed strains that help eliminate complex organic waste molecules.

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