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

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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.

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 widespread 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 Amerindi ans were substantially less diverse than in non-Amerindi ans, *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 (Cephass 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<sup>T</sup>) and *N. bacilliformis* (CCUG 50611) are rod-shaped, *N. animaloris* (NCTC 12228<sup>T</sup>) and *N. zoodegmatis* (NCTC 12230<sup>T</sup>) are coccobacilli and *N. canis* (CCUG 56775<sup>T</sup>), *N. mucosa* (CCUG 805), *N. subflava* (CCUG 801) and *N. cinerea* (CCUG 346<sup>T</sup>) 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 macaca 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. flavescens 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

<table>
<thead>
<tr>
<th>Species</th>
<th>Morphology</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>N. weaveri</td>
<td>Bacillus</td>
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<td>N. elongata</td>
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<td>N. shayegani</td>
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<td>Cocccobacillus</td>
<td>Ganière et al. (1995)</td>
</tr>
<tr>
<td>N. zoodegmatis</td>
<td>Cocccobacillus</td>
<td>Ganière et al. (1995)</td>
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<tr>
<td>N. tadorna</td>
<td>Diplcococcus</td>
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<tr>
<td>N. canis</td>
<td>Diplcococcus</td>
<td>Berger (1962)</td>
</tr>
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<td>N. denitrificans</td>
<td>Diplcococcus</td>
<td>Berger (1962)</td>
</tr>
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<td>N. animalis</td>
<td>Diplcococcus</td>
<td>Berger (1960)</td>
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<td>N. dentiae</td>
<td>Diplcococcus</td>
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<td>N. iguanae</td>
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</tr>
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<td>N. wadsworthii</td>
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</tr>
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<td>N. macaca</td>
<td>Diplcococcus</td>
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<td>N. sicca</td>
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<td>Shaw (1932)</td>
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</tr>
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<td>N. subflava</td>
<td>Diplcococcus</td>
<td>Benson et al. (1928)</td>
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<td>N. lactamica</td>
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<tr>
<td>N. skkuensis</td>
<td>Coccus</td>
<td>Park et al. (2012)</td>
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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.

<table>
<thead>
<tr>
<th>Animal host</th>
<th>Isolation site</th>
<th>Species*</th>
<th>Method</th>
<th>Reference</th>
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<tr>
<td>Dog</td>
<td>Nose</td>
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<td>Clapper &amp; Meade</td>
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<td></td>
<td>Throat</td>
<td><em>N. flavescens</em></td>
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<td><em>N. sicca</em></td>
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<td>CDC group M-5</td>
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<td><em>N. mucosa</em></td>
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<td><em>N. flavescens</em></td>
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*PP, polysaccharide producing; NPP, non-polysaccharide producing.
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<tr>
<td>Common iguana (Iguana iguana)</td>
<td>Tongue</td>
<td>N. sicca</td>
<td>Culture-dependent</td>
<td>Plowman et al. (1987)</td>
</tr>
<tr>
<td>American black vulture (Coragyps atratus)</td>
<td>Faeces immediately after defecation</td>
<td>N. mucosa and two unknown Neisseria species</td>
<td>Culture-dependent</td>
<td>Su et al. (2014)</td>
</tr>
<tr>
<td>Duck (Anas platyrhynchos or its hybrid with Anas superciliosa)</td>
<td>Caecum</td>
<td>N. flavescens</td>
<td>Culture-dependent</td>
<td></td>
</tr>
<tr>
<td>Northern bobwhite (Colinus virginianus)</td>
<td>Cloaca</td>
<td>N. flavescens</td>
<td>Culture-dependent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. sicca</td>
<td>Culture-dependent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. meningitidis</td>
<td>Culture-dependent</td>
<td>Wang (2011)</td>
</tr>
<tr>
<td>Gaoyou sheldrake</td>
<td>Liver</td>
<td>N. tardona</td>
<td>Culture-dependent</td>
<td>Wang et al. (2014)</td>
</tr>
<tr>
<td>Pekin duck</td>
<td>Liver</td>
<td>Neisseria sp. AH-N10</td>
<td>Culture-dependent</td>
<td>Dewar et al. (2013)</td>
</tr>
<tr>
<td>Macaroni and little penguins</td>
<td>Faeces from rectal swabs</td>
<td>Neisseriacae</td>
<td>Culture-independent</td>
<td>Boissière et al. (2012)</td>
</tr>
<tr>
<td>Mosquito (Anopheles gambiae)</td>
<td>Midgut</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Sharma et al. (2014)</td>
</tr>
<tr>
<td>Mosquito (Anopheles culicifacies)</td>
<td>Salivary gland</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Valiente Moro et al. (2013)</td>
</tr>
<tr>
<td>Mosquito (Aedes albopictus)</td>
<td>Whole body homogenate</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Förster et al. (2007)</td>
</tr>
<tr>
<td>Fly (12 species)</td>
<td>Body surface</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Wei et al. (2013)</td>
</tr>
<tr>
<td>House fly (Musca domestica)</td>
<td>Pupa</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Andreotti et al. (2011)</td>
</tr>
<tr>
<td>Cattle tick (Rhipicephalus microplus)</td>
<td>Adult male, egg</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Jeyaprakash et al. (2003)</td>
</tr>
<tr>
<td>African honeybee (Apis mellifera scutellata)</td>
<td>Abdomen</td>
<td>A species most closely related to N. meningitidis and S. muelleri</td>
<td>Culture-independent</td>
<td></td>
</tr>
<tr>
<td>Common woodlouse (Porcellio scaber)</td>
<td>Hindgut</td>
<td>N. perflava</td>
<td>Culture-independent</td>
<td>Kostanješ et al. (2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. mucosa</td>
<td>Culture-independent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. flavescens</td>
<td>Culture-independent</td>
<td></td>
</tr>
</tbody>
</table>
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 dentrificans 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 Neisseriaceae 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 Neisseriaceae was found in both the king and little penguins dependent on the moulting stage, indicating the abundance of Neisseriaceae 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 caecum while 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 gonococcal 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 (Boissiere 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 muenleri, 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 (Kostanjsˇek et al., 2006).

**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 (Swain & Martin, 2007; Tzeng 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**

<table>
<thead>
<tr>
<th>Isolation site</th>
<th>Species</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil</td>
<td>N. sicca</td>
<td>Culture-dependent</td>
<td>Sakai et al. (1996)</td>
</tr>
<tr>
<td>Contaminated water, soil and sediment</td>
<td>Neisseria</td>
<td>Culture-dependent</td>
<td>Carrillo-Pérez et al. (2004)</td>
</tr>
<tr>
<td>Water and sediment</td>
<td>N. mucosa</td>
<td>Culture-dependent</td>
<td>Thavasi et al. (2007)</td>
</tr>
<tr>
<td>Oil-polluted soil</td>
<td>N. sicca</td>
<td>Culture-dependent</td>
<td>Xu et al. (2014)</td>
</tr>
<tr>
<td>Biofilter packing material</td>
<td>Neisseria</td>
<td>Culture-dependent and -independent</td>
<td>Borin et al. (2006)</td>
</tr>
<tr>
<td>Showerhead biofilms</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Feazel et al. (2009)</td>
</tr>
<tr>
<td>Mattress dust</td>
<td>N. meningitidis</td>
<td>Culture-independent</td>
<td>Ege et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>N. mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N. subflava</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House dust</td>
<td>Neisseria</td>
<td>Culture-independent</td>
<td>Konya et al. (2014)</td>
</tr>
</tbody>
</table>
Table 4. Summary of infections attributed to commensal *Neisseria* species

<table>
<thead>
<tr>
<th>Species</th>
<th>Case report(s)</th>
<th>Reference</th>
</tr>
</thead>
</table>
| *N. weaveri*    | **Septicaemia**: 69-year-old male with type 2 diabetes, after dog bite  
**Lower respiratory tract infection**: 60-year-old male with 15-year bronchiectasis  
**Peritonitis**: 35-year-old male after 3 months continuous ambulatory peritoneal dialysis due to end-stage renal disease | Carlson *et al.* (1997) |
| *N. canis*      | **Fever**: 36-year-old healthy female after a cat-bite, mixed culture with *P. multocida*  
**Purulent wound and cellulitis**: 50-year-old healthy male after treading on a dog bone  
**Long-term respiratory tract infection**: 66-year-old male poodle owner with chronic obstructive pulmonary disease complicated by bronchiectasis | Guibourdenche *et al.* (1989) |
| *N. animaloris* | **Infection following animal bite**: multiple cases  
**Chronic otitis media**: 36-year-old male after ears licked by dog | Holmes *et al.* (1990) |
| *N. zoodegmatis*| **Infection following animal bite**: multiple cases  
**Skin ulceration**: 27-year-old male former drug addict with AIDS | Holmes *et al.* (1990) |
| *N. bacilliformis*| **Subacute endocarditis**: 47-year-old male with heart murmur and peripheral facial nerve palsy  
**Endocarditis**: 60-year-old male with hypertension  
**Endocarditis and septicaemia**: 30-year-old male with known hypertrophic obstructive cardiomyopathy, treated with verapamil | Masliah-Planchon *et al.* (2009) |
| *N. elongata*   | **Osteomyelitis**: 49-year-old healthy male 10 months after incisor tooth abscess de-roof  
**Endocarditis**: 54-year-old healthy male 4 months after a dental treatment  
**Endocarditis and septicaemia**: 30-year-old male with known hypertrophic obstructive cardiomyopathy, treated with verapamil | Garner & Briend (1986) |
| *N. subflava*   | **Meningitis and septicaemia**: Five cases in children  
**Bacteraemia**: 61-year-old female, 12 years after a renal transplant with low blood polymorphonuclear leukocytes due to steroid treatment  
**Endocarditis**: 49-year-old woman, 1 year after prosthetic mitral valve implant  
**Co-infection with *H. pylori* to trigger lymph follicle formation in stomach**: multiple cases | Lewin & Hughes (1966) |
| *N. flavescens* | **Endocarditis**: 82-year-old female with type 2 diabetes, aortic sclerosis and hypertension  
**Septicaemia**: 20-year-old healthy female, 7 days after dental surgery  
**Necrotizing pneumonia and empyema**: 58-year-old male with type 2 diabetes, hypertension and 40-year smoking history | Sinave & Ratzan (1987) |
| *N. mucosa*     | **Meningitis**: 33-year-old female, after ventriculoperitoneal shunt implant  
**Endocarditis**: 21 cases  
**Septicaemia**: 71-year-old male, 1 year after mitral and aortic valve replacement  
**Visceral botryomycosis**: 20-year-old male with chronic granulomatous disease | Strotka *et al.* (1991) |
| *N. sicca*      | **Endocarditis**: 17 cases mostly associated with mitral valve replacement  
**Meningitis**: 44-year-old female following intracranial haemorrhage and ventriculostomy tube placement  
** Conjunctivitis**: 79-year-old female with no history of trauma or surgery | Sommerstein *et al.* (2013) |
| *N. sikkimensis*| **Fever and foot ulcer**: 50-year-old male with type 2 diabetes, suffering from complications  
**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 | Lee *et al.* (2010) |
| *N. cinerea*    | **Peritonitis**: 38-year-old male with type 2 diabetes, 2 years after end-stage renal disease and CAPD  
**Neonatal conjunctivitis**: new born, from mother during birth  
**Bacteraemia**: 47-year-old male, underlying ethanol abuse and polymicrobial sepsis | Taegtmeyer *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, 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, acute 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 rhinocerous 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 (Crielard 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 A1, which are protective against atherosclerosis. Moreover, *N. mucosa* has been found to be present in sixfold higher amounts among obese participants.

### Table 4. cont.

<table>
<thead>
<tr>
<th>Species</th>
<th>Case report(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N. lactamica</em></td>
<td>Arthritis and septicaemia: 60-year-old male, immune suppressed by myeloma and corticosteroids</td>
<td>Everts et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Cavitary lung disease: 64-year-old male, 2 years after a cadaver kidney allograft</td>
<td>Zavascki et al. (2006)</td>
</tr>
<tr>
<td></td>
<td>Bacteraemic pneumonia: 42-year-old male with 4 year history of HBV-associated Child C liver cirrhosis and 20-year smoking history</td>
<td>Wang et al. (2006)</td>
</tr>
</tbody>
</table>
compared with normal weight individuals (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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