Porphyromonas spp. have an extensive host range in ill and healthy individuals and an unexpected environmental distribution: a systematic review and meta-analysis.

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ABSTRACT

Studies on the anaerobic bacteria *Porphyromonas*, mainly focused on *P. gingivalis*, have revealed new bacterial structures, metabolic pathways, and physiologic functionalities. *Porphyromonas* are mainly described as being associated with mammals and involved in chronic oral infections and secondary pathologies such as cancers or neurodegenerative diseases. In this review, we collected and analyzed information regarding *Porphyromonas* isolation sites and associated conditions and showed that *Porphyromonas* are detected in numerous pristine and anthropic environments and that their host range appears wider than previously believed, including aquatic animals, arthropods, and birds, even if their predominant hosts remain humans, pets, and farm animals. Our analyses also revealed their presence in multiple organs and in a substantial proportion of healthy contexts. Overall, the growing numbers of microbiota studies have allowed unprecedented advances in the understanding of *Porphyromonas* ecology but raise questions regarding their phylogenic assignment. In conclusion, this systematic and meta-analysis provides an overview of current knowledge regarding *Porphyromonas* ecological distribution and encourages additional research to fill the knowledge gaps to better understand their environmental distribution and inter- and intra-species transmission.

KEYWORDS: *Porphyromonas,* host, organ, ecological distribution

Introduction

The study of anaerobic bacteria, one of the oldest life forms, could enhance our knowledge regarding life origins [1]. These microorganisms are characterized by atmospheric oxygen intolerance [2], which hinders their isolation and culture [3]. In addition, their high nutritional requirements and slow growth [4] hamper evaluation of their metabolism, physiology, genetics, and ecology. Nevertheless, recent studies of animal and environmental microbiota have emphasized the importance of generating and integrating knowledge about anaerobic microorganisms [5,6] owing to their prevalence [7] and roles in microbial communities [1,8].

The Bacteroidetes phylum is predominant among human [9] and veterinary-associated microbiota [10] and, to a lower extent, in environmental communities [11]. This group exhibits novel features [12] such as their type IX secretion system [13,14] and type V fimbriae [15], both described for the first time in genus *Porphyromonas*. In 1921, Oliver and Wherry described black colonies on solid medium containing blood and proposed the name *Bacteroides melaninogenicum* [16]. In the 1970s and 1980s, this species was divided into three subspecies: *B. m. melaninogenicus*, *B. m. intermedius*, and *B. m. asaccharolyticus* [17] along with two others termed *B. m. macacae* [18] and *B. m. levii* [19]. This group was then renamed *Bacteroides levii*, *B. macacae*, and *B. asaccharolyticus* and the latter subsequently subdivided into two subgroups: *B. asaccharolyticus* and *B. gingivalis* [19,20], and a fifth species, *Bacteroides endodontalis*, was later described [21].

In 1988, Shah and Collins proposed creating a new genus, *Porphyromonas*, to group *Porphyromonas asaccharolytica, P. gingivalis*, and *P. endodontalis* [22]; subsequently, both *Porphyromonas macacae* [23] and *Porphyromonas levii* [24] were reclassified into this genus. The taxonomy of *P. macacae* was confusing until the mid 1990s, with two close species designated as *P. macacae* isolated in 1980 from macaques [18] and *P. salivosa* isolated in 1987 from cats [25]. These were considered as representing two distinctive heterotypic biovars [23,26,27], but are now considered a single species [28,29].

Between 1992 and 1994, six new species were described: *P. circumdentaria* [28], *P. canoris* [30], *P. cangingivalis* [31], *P. crevioricanis*, and *P. gingivicanis* [32]. Finally, a sixth non-pigmented species initially called *Oribaculum catoniae* [33] was renamed *Porphyromonas catoniae* [34]. In 2001, Fournier *et al.* divided *P. gingivalis* into *P. gingivalis* (human strains) and *P. gulae* (animal strains) [35]. Finally, eight new species completed the list: *P. uenonis* [36], *P. somerae* [37], *P. bennonis* [38], *P. pasteri* [39], *P. pogonae* [40], *P. bronchialis* [41], *P. loveana* [42], and *P. katsikii* [43]. Notably, *Falsiporphyromonas endometrii*, described in

2014 [44], is considered as a *Porphyromonas* in this study. Moreover, *P. canis* [45], and *P. cansulci* [31] have been reassigned respectively to *P. gingivicanis* [46], and *P. crevioricanis* [47]. These changes may cloud the analysis of the species, especially when some recent publications still use the old names (e.g. see [48–50]).

Most of the described *Porphyromonas* species are associated with mammal oral microbiota and implicated in pathological processes such as periodontitis [46,50,51]. Recently, *P. gingivalis* has been cited in a number of studies for its possible role in orodigestive cancers [52–54]. Other studies suggest contributions of *P. somerae* in endometrial cancer [55], *P. asaccharolytica* in colorectal cancer [56,57], and *P. endodontalis* in gastric adenocarcinoma [58]. Notably, *P. pasteri* was inversely correlated with cancer progression in oral squamous cell carcinoma [59].

In this context, the purpose of this review was to clarify the ecological distribution of *Porphyromonas*. To address this issue, we analyzed 844 studies, focusing on the sites (e.g., organ, host, and environment) and associated conditions (e.g. pathologies vs health) of isolation.

Material and methods

The literature search was conducted in accordance with the PRISMA [60] using a four-step strategy (Figure S1):

Question formulation and checking for existing reviews

When searching for reviews summarizing knowledge on the *Porphyromonas* genus, their hosts, infected organs, and associated pathologies, we noted that apart from *P. gingivalis*, no literature review existed. To our knowledge, this review is the first on this subject.

Searching and selecting the relevant studies

Three databases, PubMed, Google Scholar and Google image were searched to retrieve all records relevant to the study. The search was limited to publications after 1988, date of *Porphyromonas-Bacteroides* separation, with the exception of 2 articles describing *P. circumdentaria* and *P. macacae* [18,20]. Documents regarding *P. gingivalis* in the human oral sphere were excluded. The search was performed using key terms [All fields] in various combinations using a Boolean search technique as follows: 1) "*Porphyromonas*" AND one of the 20 species (e.g. "*Porphyromonas*" AND "*gulae*"); 2) "*P.*" AND one of the 20 species; 3)

"*Porphyromonas*" NOT *gingivalis*; and 4) "*Porphyromonas*" OR "P." AND "*gingivalis*" NOT "oral".

Peer-reviewed studies were retrieved including scientific articles, poster (n=4), abstracts, and conference proceedings along with theses. Review articles, opinions, editorials, and blogs were not included. Only studies written in English and French (n=4) were considered. Relevant results were downloaded, and their reference lists manually checked to identify missing documents using the search terms mentioned above. Duplicate records were deleted. Finally, 844 unique studies were included.

Data extraction

Information was organized in synthesis tables (Table S1 to S5) that included the *Porphyromonas* species name, organ or ecosystem as well as host or place of isolation, study authors and publication year, sample types, and situation of isolation (pathology or health status). Both authors independently assessed each study. Due to their very large number, references relating to these tables are not cited in this text but in the additional tables.

Data analysis

Hosts were categorized into three large taxonomic groups: most frequently mentioned hosts (humans, pets, farm animals and monkeys), aquatic animals, and less common hosts like rodents, birds, and arthropods. Organs were categorized into 9 major categories (Figure S2). *Porphyromonas* species names received an acronym (e.g. GUL for *P. gulae*, Figure 1 and Table S1). For the meta-analysis, bioinformatics and statistical analyses were carried out. The number of publications associated with a specific host, organ, and pathology were calculated for each *Porphyromonas*. The number of cases could not be utilized as this information is missing in the vast majority of articles. The statistical analysis was carried out using R Studio 1.2.5029 and R packages for correlation map and network generation (corrplot [61] and corrr R [62]); factorial correspondence analysis [63], hierarchical clustering [64] (FactoMineR [65] and factoextra [66]) and graphics generation (webr [67], wordcloud [68], and ggplot2 [69]).

When nucleotide sequences were accessible, we checked the taxonomic assignment using BlastN or mapping against *Porphyromonas* 16S and whole-genome in-house databases. For 16S rDNA analysis, sequences were extracted manually from each genome, the phylogenetic tree built using PhyML [70] (substitution model K80, bootstrap=20) based on MAFFT alignment [71] (algorithm: G-INS-1, scoring matrix: 200PAM/k=2), the evolutionary model

selected by Modeltest [72] (TPM3+I+G), and the corresponding distance matrix visualized using the superheat R package [73].

Results and discussion

Information sources

The 21 recognized *Porphyromonas* species are described in an extremely variable number of publications (Figure 1, Table S1). Over 90% of the documents focused on *P. gingivalis* in human oral pathologies. Consequently, the vast majority of current knowledge about *Porphyromonas* actually relates to human oral *P. gingivalis*, which is unlikely to represent the comprehensive genus biology. In the remaining 10% (844 documents), 407 documents described *Porphyromonas* without attribution of species (termed *P.* spp.). The 437 articles with species descriptions are also distributed unevenly with over half limited to three species: *P. asaccharolytica*, *P. gingivalis* in animal or non-oral human isolates, and *P. endodontalis*. Conversely, only the initial description is available for two species (*P. bronchiolis* and *F. endometrii*).

Additionally, publication frequency for each species is uneven (Figure S3). *P. gingivalis* (in the oral human context) registers hundreds of publications per year, whereas publication frequency for other *Porphyromonas* is variable and often minimal (averaging <10 papers annually). Such differences lead to a bias in the knowledge of *Porphyromonas* biology, with little if any information being produced for 20 non-*P. gingivalis* species. Nevertheless, we observed a general trend of increased publication frequencies since 2014, which corresponds to the application of next generation sequencing (NGS) in *Porphyromonas* studies (Figure S4). This technology has become an invaluable tool for their ecological study, as discussed below.

Environmental Porphyromonas

Notably, 103 scientific articles state the presence of *Porphyromonas* in environmental samples, in the vast majority with no species assignment except in 13 articles that proposed a species name based on the "best match" (Table S2). To verify these "best hits", we performed a new BlastN search and confirmed only *P. gingivalis* found on indoor climbing walls [74] and *P. asaccharolytica* in cow manure [75] whereas for three studies [76–78], we identified *Macellibacteroides fermentans* and *Fermentimonas caenicola*, respectively instead of *Porphyromonas*. However, most studies do not provide access to raw data and taxonomic designation cannot be verified. This highlights the importance of depositing sequencing data in

open databases to allow reproducibility and re-analysis, with the fast-growing databases enabling updates of the results. Moreover, when the "best hits" results are low, especially in the Porphyromonadaceae family for which taxonomy is frequently revised [79], it is therefore preferable to limit the description to the genus level. Owing to such possible errors in species assignment and lack of verification capability, we chose to consider environmental *Porphyromonas* as unknown species (*P.* spp.).

A non-exhaustive description of the environmental diversity of *Porphyromonas* is presented in Figure 2 and Table S2. In pristine environments (27%), *Porphyromonas* have been isolated from air samples (4%); from soils (10%) like agricultural lands and crops, alpine meadows, sediments and subseafloor, and in fresh- and sea- water (13%). In anthropogenic environments (73%), *Porphyromonas* have been detected in healthcare facilities as well as in indoor buildings and transport systems that constitute potential sites for microbial transmission between human and animal populations. Additionally, *Porphyromonas* were detected in various personal use objects. Finally, the most important source of environmental *Porphyromonas* derives from waste-management settings.

In summary, the environmental component of *Porphyromonas* is far from negligible. In some studies, *Porphyromonas* constitute "rare taxons" (< 1%) whereas in others they are abundant and described as part of the "core microbiome". Such environmental detection of *Porphyromonas* raises issues including whether they result from cross-contamination or are persistent in the environment or continually transmitted by oral and/or fecal material. These questions are inherent in all studies carried out by detecting DNA (PCR or NGS) that do not guarantee viability of the identified bacteria.

This review does not answer these questions but suggests that *Porphyromonas* have a capacity to persist in pristine and man-polluted environments, indicative of resistance to stressors such as atmospheric oxygen, UV radiation, or nutrient depletion, possibly via dormancy mechanisms leading to viable non-cultivable forms (VBNCs). It is also possible that in free-form, biotic interactions are harmful to *Porphyromonas* as these are not very competitive but in favorable situations such as biofilms, these bacteria are protected in a nutrient-rich microenvironment and may benefit from cooperation with other bacteria to maintain and/or thrive. Thus, environmental niches may be temporarily utilized by *Porphyromonas*, which then re-colonize and re-infect human or animal hosts.

Host-associated Porphyromonas

All *Porphyromonas* species, except for *P. bronchialis* and *Falsiporphyromonas* described only a few times, are detected in both disease and health conditions, in various proportions (Figure 3). Until 2012, *Porphyromonas* research had been focused on clinical microbiology and therefore biased toward pathological contexts with scarce descriptions in healthy contexts. This bias gradually disappeared concomitant with recent "without *a priori*" NGS studies that reported proportions of *Porphyromonas* spp. (*P.* spp., Figure S3) at 58.7% in healthy states versus 41.3% in disease conditions. This may be interpreted as these species constituting not true pathogens (according to Pasteur or Koch) but rather key bacteria ("keystone pathogen" or "alpha bug theory" [80,81]), orchestrating, even at low abundance, host immune response or serving as pathobionts ("bacterial passengers theory" [82]) that profit from altered homeostasis to thrive and trigger disease. Evaluation of the frequency of the major pathologies described for all species (Figure 4) reveals the preponderance of inflammatory diseases (suffix "-itis"), followed by cancers, degenerative and autoimmune diseases. These observations confirm a complex pathological pattern for *Porphyromonas* including an assortment of primary diseases and secondary morbidities.

In the literature, *Porphyromonas* host range is often dichotomic with opposing human and veterinary strains (e.g. see [83–85]), which may be interpreted as host specificity. However, it is important to reassess host range to address several major epidemiological issues including whether two or more *Porphyromonas* species can cohabite within a single microbiota, whether zoonosis is possible, and, if so, whether this provokes colonization, infection, adaptation, and propagation to new hosts or only transitory infection. Answers to these questions are necessary to assess the possible threat to public health and food safety. For example, the presence of *Porphyromonas* in bovine milk has been described [86,87] but it remains unknown whether **its** consumption may result in exogenous transmission. The possibility of *Porphyromonas* transfer between humans and pets is also unresolved. In order to reexamine *Porphyromonas* host range, we classified all animal isolation sources as minority/newly cited or main/historically known hosts, as follows.

Minor or newly cited hosts of Porphyromonas

Minor *Porphyromonas* hosts include aquatic wildlife (Table S3), arthropods, birds, small and/or wild mammals (Table S4). Briefly, in aquatic wildlife, *Porphyromonas* can survive and multiply in amoebas and endure physical and chemical stresses in their cysts. This intracellular existence can help *Porphyromonas* escape from macrophages in healthcare

facilities [88]. Marine life interactions have been noted in ciliates, corals, copepods, and oysters, playing a possible role in *Porphyromonas* survival and potential transfer along the food chain, as these bacteria are also found in fish, cetaceans, and penguins. This presence in aquatic animals should be contextualized with their presence in pristine aquatic environments. *Porphyromonas* were also detected in intestinal microbiota of arthropods (ectoparasites and insects), in birds' intestinal and respiratory microbiota and appears frequent in the oral, genital, anal, ocular, and nasal microbiota of wild and captive marsupials and mammals.

Frequent or frequently studied hosts of Porphyromonas

The major studied hosts all constitute mammals; in descending order: humans, dogs, cats, cattle, sheep, pigs, and monkeys. Using a contingency table for each *Porphyromonas* species phenotypic marker (health status, host, and organ, Table S1), significant correlations were visualized as a correlogram (Figure 5A) which revealed six isolated species, alone or in pairs. With the exception of *P. levii*, we suspect that this was largely due to the small number of publications (from one to six). The segregated species are as follows.

P. levii. Previously known as *Bacteroides melaninogenicus subsp. levii* then as *Bacteroides levii* [19] and reclassified as *Porphyromonas* in 1995 [24]. To avoid confusion, only publications after 1995 were considered for this species. However, some publications after 1995 still used the old *Bacteroides levii* name [89] or the terminology *P. levii*-like organisms (PLLO) [90,91], which might correspond to *P. somerae* [27,37,92]. For example, only one publication recorded *P. levii* in human vaginitis [93], a typical isolation site of *P. somerae*; this may therefore be a case of misidentification. Considering only accurate *P. levii* designations, we found that this species is quite specific to ovine infections [94] (Table S1). Despite its high prevalence, *P. levii* distribution within lesions suggests its role as a secondary colonizer rather than a main etiologic agent [95]. Additionally, in some cases, its presence in non-affected animals has been described [96,97]. As this species was initially isolated from healthy cattle rumen [19,98] and is occasionally re-detected in this organ [99,100], it can be hypothesized that the skin and genital colonization might be due to fecal contamination and/or hematogenous propagation [101].

Falsiporphyromonas endometrii. Originally isolated from cow endometrium [44] and in intestinal microbiota from sows, this species had been relegated to a new genus at the time of

this publication as its phylogenetic distance from other *Porphyromonas* was deemed excessive. However, rebuilding the rRNA 16S tree and distance matrix (Figures 5B & 5C) indicated a *Porphyromonas* typical identity percentage. We therefore considered *Falsiporphyromonas* as a *Porphyromonas* in the absence of an official reclassification. Moreover, searching against BLAST gave *Porphyromonas* sp. 2069 and 2070 along with *P. levii* [102] and *Porphyromonas* sp. clone 1M9 [103] as best hits.

P. katsikii. Published only once after its isolation from sheep with pneumonia. BLAST search using **its** 16S sequence (accession number: KM360064) revealed four hits (99% identity) corresponding to uncultured *Porphyromonas* sp. isolated from the uterus of healthy or metric cows [97].

P. loveana. Cited in three articles, two of which recorded five strains in Australian marsupials and one defining two strains in New Zealand sheep. Only partial 16S gene sequences are available from the Australian strains that form an Oceania endemic group (97 to 100% identity).

P. pogonae. Described in six articles, first isolated from different polymicrobial infections in *Pogona* [104]. This species has also been described from the wounds of a crowned crane (*Balearica* sp.) and in human infections [40,105–107].

P. bronchialis. Only the initial description article for this species is available as a source of information, including four strains isolated from bronchial liquid from a single patient [41]. No nucleic acid sequence is available.

For the remaining 15 species, correspondence analysis using a host contingency table (Figure 6A) revealed a clear separation in 4 clusters (axis 1, 80% variance) between species dominant in human versus those of pets (Figure 6B):

Cluster 1 contains five species essentially described in humans: *P. uenonis* and *P. somerae* yet described in cattle infections [102,108], and *P. asaccharolytica*, *P. catoniae*, and *P. endodontalis* also described in pets, cattle, and primates.

P. gingivalis, clusters with *P. pasteri* and *P. bennonis* in a strongly human-associated group (Cluster 2). However, *P. pasteri* (exclusively human) and *P. bennonis* (also cited in pig feces [109]) are poorly studied (Figure 1).

P. gulae, *P. gingivalis* closest relative (Figure 5B), grouped in Cluster 4 with *P. macacae*, *P. canoris*, and *P. circumdentaria*. As such, *P. gingivalis* and *P. gulae* appear as two ecotypes separated according to number of human and canine cases [110,111] and distinguishable by the catalase test, *P. gulae* being positive and *P. gingivalis* negative [35]. Nevertheless, these two species contain similar virulence factors [85,112]. *P. gulae* can invade human cells *in vitro* [113] but with less adherence to human cells than *P. gingivalis* [114].

Some articles recorded *P. gulae* in humans. A study showed that its high prevalence in aborigines, may be associated with their traditional diet (primate meat) and/or use of capuchin as pets, facilitating transmission from primate to human. Notably, the authors hypothesize that *P. gulae* may be a competitor of *P. gingivalis* and that both species might rarely or inefficiently cohabit [115]. Yet, both species have been identified in biofilms from periodontitis [116]. Moreover, *P. gulae* have been detected in the oral cavities and skin of dog owners, which may potentially result from dog-to-human transfer [117,118], poster). Conversely, *P. gulae* was not detected in cat owners [119]. Additionally, *P. gulae* have been reported in fecal samples from patients with colorectal cancer [120] and with *P. gingivalis* in cervical microbiota from infertile women [121]. It is difficult to synthesize colonization of humans by *P. gulae* as few studies exist and as this species is highly similar to *P. gingivalis*. Therefore, several questions remain, such as whether the absence of co-detection is legitimate or owing to inadequate analyses that underestimate the presence of *P. gulae* in human microbiota, or, if such cohabitation is indeed rare. However, if both species can coexist in humans, the issue of *P. gulae* zoonotic transfer (Table S1; Fig 6B) should be addressed considering the involvement of *Porphyromonas* in oncologic and neurologic diseases.

Correspondingly, *P. gingivalis* has been reported in animal oral cavities either with or without periodontitis, and in bite wounds and fecal material (Table S1). However, as *P. gingivalis* remains isolated predominantly from human medicine contexts**,** its study in animals is therefore necessary to elucidate whether these reports correspond to opportunistic colonization, occasional and transitory transfer from human to animals, or whether this species is not exclusively human-based.

All canine and feline species clustered with *P. gulae* (Cluster 4, Fig 6B)**,** and are also occasionally reported in humans (from 6 to 15% of cases). *P. canoris* in human skin (Table S1), *P. circumdentaria* in healthy liver biopsies [122] and in fecal and genital microbiomes [121,123]. *P. macacae* have been reported in breast cancer [124] and infected wound bites

[27,125,126], which was expected as this species is frequently identified in pet oral microbiota (Table S1).

The last cluster (Cluster 3, Fig 6B) groups *P. gingivicanis*, *P. crevioricanis*, and *P. cangingivalis*, originally described in dog oral microbiota but also detected in cat, human, and cattle pathologies (Table S1).

In conclusion, we found that *Porphyromonas* was present in almost all animal orders. This information raises new questions about their epidemiology and host-specificities. Indeed, the only studies regarding *Porphyromonas* host-to-host transmission are between humans, specifically interfamily transmission [127–135], and from oral sources, with saliva as the vehicle [136]. Epidemiological studies of *Porphyromonas* in animals do not appear to be a priority. However, domestic mammals (cattle, cats, and dogs) live in very close association with their owners and all their secretions (saliva, urine) are present in the everyday environment. This review thus highlights the necessity for a rigorous reassessment of *Porphyromonas* host specificities.

Moreover, although numerous studies have associated these bacteria with clinical observations, mostly in human dentistry, NGS studies in the past decade have revealed a much wider host range. Prior to these approaches, classical culture-based have been insufficient to broaden our knowledge regarding *Porphyromonas* host diversity, as these bacteria are fastidious, slow growing, and produce low biomass. The presence of *Porphyromonas* across numerous and varied environments renders it necessary to determine whether they constitute generalist environmental pathogens or specialized opportunists that may briefly transfer to other reservoirs. To explore these issues, we reviewed *Porphyromonas* distribution in different organs, both in healthy and pathological conditions.

Organ distribution of *Porphyromonas*

The distribution of *Porphyromonas* in cellular compartments is likely indicative of their colonization mechanism. To summarize the information, we classified the anatomical sites in nine categories with associated pathological or healthy conditions (Figure S2).

The objective of this investigation was to clarify and extend our knowledge regarding their cellular specificities. Generally, the scientific literature simplifies the findings and usually describes *Porphyromonas* species as expressly localized in specific body sites; e.g. *P. gingivalis* and *P. endodontalis* in the oral cavity, *P. uenonis* in the gut, and *P. somerae* in the genital tract. A contingency table registering the number of articles citing each of the nine organ categories

was used to generate a hierarchical clustering and waffle plots (Figure 7). Analysis of these plots revealed that none of the 15 species of *Porphyromonas* exhibits organ specificity but rather preferences for certain anatomical sites.

P. asaccharolytica and *P. gingivalis*, the two most published *Porphyromonas* (Figure 1), are the only species to be found in all 9 sites, albeit at variable proportion. This suggested that the number and diversity of publications constitute important factors that likely bias the results of less-reported species. Nevertheless, currently available data reveal three different types of profiles. The first cluster (Figure 7) corresponds to "multiple organ" behavior involving *P. asaccharolytica*, *P. somerae*, *P. bennonis*, and *P. uenonis*. The second cluster includes *P. macacae*, *P. cangingivalis*, *P. canoris*, *P. circumdentaria*, and *P. crevioricanis* found in the oral cavity and skin. As these species are often isolated from pets, the hypothesis of secondary opportunistic infection of bite and scratches wounds by oral *Porphyromonas* after licking represents the most obvious route of transmission. Finally, the third group (Figure 7) includes essentially oral bacteria such as *P. gulae*, *P. gingivalis*, *P. endodontalis*, *P. gingivicanis*, *P. catoniae*, and *P. pasteuri*, which are also occasionally detected in other organs.

This descriptive analysis suggested the capacity of *Porphyromonas* species to propagate in and on different body sites, thus allowing consideration of primary sites and various invasion routes allowing secondary colonization. However, the research needed to understand these routes of transmission is lacking. Although numerous analyses have been published regarding *Porphyromonas* adhesion to host cells, these are predominantly of *P. gingivalis*; complementary investigation must therefore be achieved for the other species. Mechanisms that allow the establishment and maintenance of an intracellular lifestyle along with the diversity of intracellular compartments used for *Porphyromonas* replication and crossing of host barriers need to be specifically studied in all species if possible. This knowledge would allow more precise definition of the threshold between *Porphyromonas* commensalism and pathogenicity, which constitutes a relevant issue as demonstrated in this review because these bacteria belong to the host microbiota and can therefore be considered commensal but can become pathogenic when they escape from their original niche or when their growth rate increases.

Concluding remarks

The initial objective of this review was to summarize the knowledge regarding the host and organ range in addition to associated conditions (pathological or healthy) for the 21 species of the *Porphyromonas* genus currently described. However, the marked heterogeneity in the

knowledge between *P. gingivalis*, the predominantly reported species with several studies per week and that of the large majority of species, associated with only 5 to 10 articles annually, along with the "exotic" species such as *P. bronchialis* or *P. katsikii* that have accumulated < 5 papers over the past 20 years, was immediately apparent. We also observed that approximately half of the eligible studies described *Porphyromonas* spp. This inevitably resulted in “gray areas” and biases that rendered the interpretation of the results difficult and imprecise. However, the number of cases of cancers or systemic diseases associated directly or indirectly with *Porphyromonas* is accumulating, in addition to the previously well documented cases of infections and inflammations. A more thorough understanding of this bacterial genus therefore appears important for enhancing human and veterinary health with various complementary experiments, as discussed throughout this review, appearing necessary to clarify the taxonomic descriptions and refine the biological characterizations of the less-reported species. The summary schematic (Figure 8) showing their presence in numerous environments, hosts, and biological niches is thus incomplete and biased but nevertheless indicates the extremely widespread albeit poorly studied ecological distribution of this important bacterial genus.

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Disclosure statement

The authors declare that they have no competing interests.

Figure legends

Figure 1. Number of documents (scientific articles, doctoral theses, posters, and conference abstracts; total = 437) related to *Porphyromonas* species. *P. gingivalis* studied in the human oral biotope (GIN_o) does not appear because its records exceeded 8000 documents. Only records citing this species in non-human (animals) or human non_oral contexts (GIN_no) are represented. Records for which the species was not identified, i.e. *Porphyromonas* spp. (*P.* spp.), are not presented (407 records).

Figure 2. Pie chart sub-categorized with a donut diagram representing the proportion of the different environments in which *Porphyromonas* were detected. Pristine environments correspond to undisturbed ecosystems and thus unmodified by human activity as opposed to anthropogenic environments, reflecting those modified by human activities.

Figure 3. Polar chart representing the proportion of records associated with each *Porphyromonas* species along with *Porphyromonas* spp. and either healthy (green) or disease (red) conditions. The total number of records corresponds to that presented in Figure 1. For *P. gingivalis*, the oral human records (GIN_o) were totaled using PubMed abstracts whereas oral and non-oral animal cases in addition to non-oral human cases (GIN_no) were fully analyzed similarly to the other *Porphyromonas* species.

Figure 4. Word cloud representing all the pathologies and/or keywords associated with all *Porphyromonas* species as recorded in this analysis. The word size corresponds its number and is proportional to the total of pathologies/keywords mentioned; colors are used in accordance with the word size (from the most frequent to the least frequent: warm colors to cool colors).

Figure 5. Relationship between *Porphyromonas* species phenotypic traits and phylogenetic relatedness. **A.** Top panel. Correlogram displaying the phenotypic correlation matrix (organ, host distribution, and pathology association). Color intensity and dot size indicate the Pearson coefficient values from light (0) to dark (1). Bottom panel. Correlation network to visualize pairwise correlations between *Porphyromonas* species inside each of the three clusters presented in the top panel. Each edge stands for a Spearman correlation > 0.90 ($p < 0.05$). Color of the edges is related to the coefficient of correlation from light to dark. Isolated species, alone or in pairs, are marked with an asterisk. **B.** 16S rDNA phylogenetic tree. The number between

453 brackets corresponds to the number of strains used to generate each consensus sequence by
454 species. Colors represent the clusters of correlograms in panel A. *P. bronchialis* is absent as its
455 16S sequence is not available. **C.** Distance matrix used for the 16S rDNA phylogenetic tree in
456 B.
457
458 **Figure 6.** Major host distribution for the three *Porphyromonas* species clusters identified based
459 on phenotypic traits. **A.** Factorial correspondence analysis of *Porphyromonas* species according
460 to the number of cases for each category of major hosts (see details in the text). **B.** Host-range
461 repartition detailed for each *Porphyromonas* species and each identified cluster. Green, Cluster
462 I; red, Cluster 2; blue, Cluster 3; purple, Cluster 4.
463
464 **Figure 7.** Hierarchical clustering of *Porphyromonas* species according to the isolation site or
465 organ separated by category (see details in Figure S4). The waffle charts reflect the relative
466 abundances in each organ group described above (one block = 1%).
467
468 **Figure 8.** Overview of *Porphyromonas* isolation and/or description in all habitats including the
469 environment and all its hosts. Within hosts, organs or body sites from which *Porphyromonas*
470 have been described are detailed.
471
472 **Supplemental Figure S1**. Preferred reporting elements for systematic reviews and meta-
473 analyzes (PRISMA), flowchart and checklist detailing documents search (from 01-1988 to 09-
474 2019) and selection process applied in this systematic review and meta-analysis about
475 *Porphyromonas* ecology.
476
477 **Supplemental Figure S2**. Categories used in this meta-analysis corresponding to the isolation
478 site or organ in which *Porphyromonas* species have been described; a full description of all
479 terms is presented for each category.
480
481 **Supplemental Figure S3**. Number of records included in this study for each *Porphyromonas*
482 species by year from 01–1988 until 09–2019. For *P. gingivalis*, the oral human records (GIN_o)
483 were totaled using PubMed abstracts whereas oral and non-oral animal cases in addition to non-
484 oral human cases (GIN_no) have been referenced based on full records for the meta-analysis,
485 as for the other *Porphyromonas* species.

Supplementary Figure S4. Number of records according to method of *Porphyromonas* identification and year. For each record included in this study, the identification method for any *Porphyromonas* isolate was classified into four categories: traditional identification and culturomics, immunologic or other wet lab method, specific 16S rDNA PCR to identify *Porphyromonas* species and related methods, and microbiota and metagenomics studies (NGS).

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