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

3

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5

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12 **ABSTRACT**

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

29

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

31

32 **Introduction**

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

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

51 In 1988, Shah and Collins proposed creating a new genus, *Porphyromonas*, to group
52 *Porphyromonas asaccharolytica*, *P. gingivalis*, and *P. endodontalis* [22]; subsequently, both
53 *Porphyromonas macacae* [23] and *Porphyromonas levii* [24] were reclassified into this genus.
54 The taxonomy of *P. macacae* was confusing until the mid 1990s, with two close species
55 designated as *P. macacae* isolated in 1980 from macaques [18] and *P. salivosa* isolated in 1987
56 from cats [25]. These were considered as representing two distinctive heterotypic biovars
57 [23,26,27], but are now considered a single species [28,29].

58 Between 1992 and 1994, six new species were described: *P. circumdentaria* [28], *P. canoris*
59 [30], *P. cangingivalis* [31], *P. crevioricanis*, and *P. gingivicanis* [32]. Finally, a sixth non-
60 pigmented species initially called *Oribaculum catoniae* [33] was renamed *Porphyromonas*
61 *catoniae* [34]. In 2001, Fournier *et al.* divided *P. gingivalis* into *P. gingivalis* (human strains)
62 and *P. gulae* (animal strains) [35]. Finally, eight new species completed the list: *P. uenonis*
63 [36], *P. somerae* [37], *P. bennonis* [38], *P. pasteri* [39], *P. pogonae* [40], *P. bronchialis* [41],
64 *P. loveana* [42], and *P. katsikii* [43]. Notably, *Falsiporphyromonas endometrii*, described in

65 2014 [44], is considered as a *Porphyromonas* in this study. Moreover, *P. canis* [45], and *P.*
66 *cansulci* [31] have been reassigned respectively to *P. gingivicanis* [46], and *P. crevioricanis*
67 [47]. These changes may cloud the analysis of the species, especially when some recent
68 publications still use the old names (e.g. see [48–50]).

69 Most of the described *Porphyromonas* species are associated with mammal oral microbiota
70 and implicated in pathological processes such as periodontitis [46,50,51]. Recently, *P.*
71 *gingivalis* has been cited in a number of studies for its possible role in orodigestive cancers [52–
72 54]. Other studies suggest contributions of *P. somerae* in endometrial cancer [55], *P.*
73 *asaccharolytica* in colorectal cancer [56,57], and *P. endodontalis* in gastric adenocarcinoma
74 [58]. Notably, *P. pasteri* was inversely correlated with cancer progression in oral squamous cell
75 carcinoma [59].

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

80

81 **Material and methods**

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

84

85 ***Question formulation and checking for existing reviews***

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

89

90 ***Searching and selecting the relevant studies***

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

98 “*Porphyromonas*” NOT *gingivalis*; and 4) “*Porphyromonas*” OR “P.” AND “*gingivalis*” NOT
99 “oral”.

100 Peer-reviewed studies were retrieved including scientific articles, poster (n=4), abstracts,
101 and conference proceedings along with theses. Review articles, opinions, editorials, and blogs
102 were not included. Only studies written in English and French (n=4) were considered. Relevant
103 results were downloaded, and their reference lists manually checked to identify missing
104 documents using the search terms mentioned above. Duplicate records were deleted. Finally,
105 844 unique studies were included.

106

107 ***Data extraction***

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

113

114 ***Data analysis***

115 Hosts were categorized into three large taxonomic groups: most frequently mentioned hosts
116 (humans, pets, farm animals and monkeys), aquatic animals, and less common hosts like
117 rodents, birds, and arthropods. Organs were categorized into 9 major categories (Figure S2).
118 *Porphyromonas* species names received an acronym (e.g. GUL for *P. gulae*, Figure 1 and Table
119 S1). For the meta-analysis, bioinformatics and statistical analyses were carried out. The number
120 of publications associated with a specific host, organ, and pathology were calculated for each
121 *Porphyromonas*. The number of cases could not be utilized as this information is missing in the
122 vast majority of articles. The statistical analysis was carried out using R Studio 1.2.5029 and R
123 packages for correlation map and network generation (corrplot [61] and corrr R [62]); factorial
124 correspondence analysis [63], hierarchical clustering [64] (FactoMineR [65] and factoextra
125 [66]) and graphics generation (webr [67], wordcloud [68], and ggplot2 [69]).

126 When nucleotide sequences were accessible, we checked the taxonomic assignment using
127 BlastN or mapping against *Porphyromonas* 16S and whole-genome in-house databases. For
128 16S rDNA analysis, sequences were extracted manually from each genome, the phylogenetic
129 tree built using PhyML [70] (substitution model K80, bootstrap=20) based on MAFFT
130 alignment [71] (algorithm: G-INS-1, scoring matrix: 200PAM/k=2), the evolutionary model

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

133

134 **Results and discussion**

135 ***Information sources***

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

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

154

155 ***Environmental Porphyromonas***

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

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

170 A non-exhaustive description of the environmental diversity of *Porphyromonas* is presented
171 in Figure 2 and Table S2. In pristine environments (27%), *Porphyromonas* have been isolated
172 from air samples (4%); from soils (10%) like agricultural lands and crops, alpine meadows,
173 sediments and seafloor, and in fresh- and sea- water (13%). In anthropogenic environments
174 (73%), *Porphyromonas* have been detected in healthcare facilities as well as in indoor buildings
175 and transport systems that constitute potential sites for microbial transmission between human
176 and animal populations. Additionally, *Porphyromonas* were detected in various personal use
177 objects. Finally, the most important source of environmental *Porphyromonas* derives from
178 waste-management settings.

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

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

195

196 ***Host-associated Porphyromonas***

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

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

224

225 *Minor or newly cited hosts of Porphyromonas*

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

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

237

238 *Frequent or frequently studied hosts of Porphyromonas*

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

245

246 *P. levii*. Previously known as *Bacteroides melaninogenicus subsp. levii* then as *Bacteroides*
247 *levii* [19] and reclassified as *Porphyromonas* in 1995 [24]. To avoid confusion, only
248 publications after 1995 were considered for this species. However, some publications after 1995
249 still used the old *Bacteroides levii* name [89] or the terminology *P. levii*-like organisms (PLLO)
250 [90,91], which might correspond to *P. somerae* [27,37,92]. For example, only one publication
251 recorded *P. levii* in human vaginitis [93], a typical isolation site of *P. somerae*; this may
252 therefore be a case of misidentification. Considering only accurate *P. levii* designations, we
253 found that this species is quite specific to ovine infections [94] (Table S1). Despite its high
254 prevalence, *P. levii* distribution within lesions suggests its role as a secondary colonizer rather
255 than a main etiologic agent [95]. Additionally, in some cases, its presence in non-affected
256 animals has been described [96,97]. As this species was initially isolated from healthy cattle
257 rumen [19,98] and is occasionally re-detected in this organ [99,100], it can be hypothesized that
258 the skin and genital colonization might be due to fecal contamination and/or hematogenous
259 propagation [101].

260

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

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

269

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

274

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

278

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

282

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

286

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

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

293 *P. gingivalis*, clusters with *P. pasteri* and *P. bennonis* in a strongly human-associated group
294 (Cluster 2). However, *P. pasteri* (exclusively human) and *P. bennonis* (also cited in pig feces
295 [109]) are poorly studied (Figure 1).

296 *P. gulae*, *P. gingivalis* closest relative (Figure 5B), grouped in Cluster 4 with *P. macacae*,
297 *P. canoris*, and *P. circumdentaria*. As such, *P. gingivalis* and *P. gulae* appear as two ecotypes
298 separated according to number of human and canine cases [110,111] and distinguishable by the
299 catalase test, *P. gulae* being positive and *P. gingivalis* negative [35]. Nevertheless, these two
300 species contain similar virulence factors [85,112]. *P. gulae* can invade human cells *in vitro*
301 [113] but with less adherence to human cells than *P. gingivalis* [114].

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

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

324 All canine and feline species clustered with *P. gulae* (Cluster 4, Fig 6B), and are also
325 occasionally reported in humans (from 6 to 15% of cases). *P. canoris* in human skin (Table S1),
326 *P. circumdentaria* in healthy liver biopsies [122] and in fecal and genital microbiomes
327 [121,123]. *P. macacae* have been reported in breast cancer [124] and infected wound bites

328 [27,125,126], which was expected as this species is frequently identified in pet oral microbiota
329 (Table S1).

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

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

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

351

352 **Organ distribution of *Porphyromonas***

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

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

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

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

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

389

390 **Concluding remarks**

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

394 knowledge between *P. gingivalis*, the predominantly reported species with several studies per
395 week and that of the large majority of species, associated with only 5 to 10 articles annually,
396 along with the "exotic" species such as *P. bronchialis* or *P. katsikii* that have accumulated < 5
397 papers over the past 20 years, was immediately apparent. We also observed that approximately
398 half of the eligible studies described *Porphyromonas* spp. This inevitably resulted in "gray
399 areas" and biases that rendered the interpretation of the results difficult and imprecise.
400 However, the number of cases of cancers or systemic diseases associated directly or indirectly
401 with *Porphyromonas* is accumulating, in addition to the previously well documented cases of
402 infections and inflammations. A more thorough understanding of this bacterial genus therefore
403 appears important for enhancing human and veterinary health with various complementary
404 experiments, as discussed throughout this review, appearing necessary to clarify the taxonomic
405 descriptions and refine the biological characterizations of the less-reported species. The
406 summary schematic (Figure 8) showing their presence in numerous environments, hosts, and
407 biological niches is thus incomplete and biased but nevertheless indicates the extremely
408 widespread albeit poorly studied ecological distribution of this important bacterial genus.
409

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416

417 **Disclosure statement**

418 The authors declare that they have no competing interests.

419

420 **Figure legends**

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

427
428 **Figure 2.** Pie chart sub-categorized with a donut diagram representing the proportion of the
429 different environments in which *Porphyromonas* were detected. Pristine environments
430 correspond to undisturbed ecosystems and thus unmodified by human activity as opposed to
431 anthropogenic environments, reflecting those modified by human activities.

432
433 **Figure 3.** Polar chart representing the proportion of records associated with each
434 *Porphyromonas* species along with *Porphyromonas* spp. and either healthy (green) or disease
435 (red) conditions. The total number of records corresponds to that presented in Figure 1. For *P.*
436 *gingivalis*, the oral human records (GIN_o) were totaled using PubMed abstracts whereas oral
437 and non-oral animal cases in addition to non-oral human cases (GIN_no) were fully analyzed
438 similarly to the other *Porphyromonas* species.

439
440 **Figure 4.** Word cloud representing all the pathologies and/or keywords associated with all
441 *Porphyromonas* species as recorded in this analysis. The word size corresponds its number and
442 is proportional to the total of pathologies/keywords mentioned; colors are used in accordance
443 with the word size (from the most frequent to the least frequent: warm colors to cool colors).

444
445 **Figure 5.** Relationship between *Porphyromonas* species phenotypic traits and phylogenetic
446 relatedness. **A.** Top panel. Correlogram displaying the phenotypic correlation matrix (organ,
447 host distribution, and pathology association). Color intensity and dot size indicate the Pearson
448 coefficient values from light (0) to dark (1). Bottom panel. Correlation network to visualize
449 pairwise correlations between *Porphyromonas* species inside each of the three clusters
450 presented in the top panel. Each edge stands for a Spearman correlation > 0.90 ($p < 0.05$). Color
451 of the edges is related to the coefficient of correlation from light to dark. Isolated species, alone
452 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.

486

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

492

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