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Dysbiosis in Parkinson's disease might be triggered by certain antibiotics

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative amyloid disorder with debilitating motor symptoms due to the loss of dopamine-synthesizing, basal ganglia-projecting neurons in the substantia nigra. An interesting feature of the disease is that most of PD patients have gastrointestinal problems and bacterial dysbiosis, years before the full expression of motor symptoms. We hypothesized that antibiotic consumption might be a contributing factor of gut microbiome dysbiosis in PD, favoring *curli*-producing *Enterobacteria*. *Curli* is a bacterial α-synuclein (αSyn) which is deposited first in the enteric nervous system and amyloid deposits are propagated in a prion like manner to the central nervous system. In addition, antibiotics result in a low-grade systemic inflammation, which also contributes to damage of neurons in enteric- and central nervous system. To support our hypothesis, by comparing PD prevalence change with antibiotic consumption data in EU countries, we found significant positive correlation between use narrow spectrum penicillin + penicillinase resistant penicillin and increased prevalence of the disease.

Introduction

According to an ancient proverb, "death lives in the belly", and with the discovery of the extensive role of gut microbiome in the development of different serious diseases, our recent knowledge should confirm this statement.

Parkinson's disease (PD) was discovered by James Parkinson 200 years ago and he treated his patients with intensive purgative drugs and observed an improvement of the symptoms, without even having any knowledge of gut flora or microbiome [1,2].

Background

PD is a slowly developing, neurodegenerative disease with serious motor- and neuropsychiatric symptoms. PD affects 2% of the global population aged over 80 years [3]. PD is currently incurable, although variety of symptomatic therapies are available. According to a recent survey, published in the Lancet [4] the number of patients diagnosed with PD has doubled in the past 25 years and their number exceeds 6 million over the world. PD is being considered as the second largest group of neurodegenerative diseases after Alzheimer's disease.

Variety of PD's symptoms are associated with loss of dopaminergic neurons in the midbrain substantia nigra, pars compacta (SNPc). These neurons innervate basal ganglia, including the striatum. Loss of dopamine in the striatum trigger cellular and synaptic alterations, which are responsible for the appearance of the motor symptoms of PD [5]. In addition to motor programming and execution, basal ganglia also participate in learning, cognition and emotion; functions, which are also affected in PD [6].

The main histopathological characteristics of PD are cell death affecting up to 70% of the dopamine secreting neurons in SNPc and presence of α-synuclein (αSyn) aggregates in the form of Lewy bodies in the remaining neurons [7]. The loss of neurons is accompanied by a significant increase of reactive microglia and A1 neurotoxic astrocytes in the substantia nigra [8,9].

The definite cause of PD is still unknown, environmental triggers in combination with genetic vulnerability factors are proposed [10]. Increased risk of PD has been associated with exposure to pesticides, consumption of dairy products, history of melanoma and traumatic brain injury, whereas a reduced risk has been reported in association with smoking, caffeine consumption, higher serum urate concentrations, physical activity, and use of non-steroidal anti-inflammatory medications [11].

PD patients experience several non-motor symptoms, including sleep dysfunction [12], anosmia [13] and gastrointestinal problems [14]. The gastrointestinal abnormalities may occur years before manifestation of motor disturbances and diagnosis of PD [14]. Recent studies confirm that neuropsychiatric conditions, including PD, which have

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classically been established as disorders of the brain also have etiologies in the gut [15]. Along these lines, recent evidence uncovered the presence of αSyn accumulation/Lewy bodies in the enteric nervous system of PD patients [16].

Gut microbiome is the largest bacterial community within the human body which significantly affects host physiology. For instance, vitamins, metabolites, hormones, immune modulators, neurotransmitters, neuropeptides produced by those bacteria which colonized the gastrointestinal (GI) tract may influence central nervous system functions through the gut-(microbiome)-brain axis [17–20]. Furthermore, certain gut bacteria such as *E. coli, Salmonella* and other strains of the *Bacteroidaceae* family produce *curli,* a functional amyloid peptide which forms extracellular fibril deposits in the GI tract to promote adhesion and colonization via resistant biofilm formation [21]. These bacterial amyloids have the ability to initiate additional αSyn deposits via cross-seeding [22] and transmit their pathogenic conformation as prions [23]. It has been proposed that GI abnormalities seen in PD patients is related to bacterial dysbiosis and curly/αSyn deposits in the enteric nervous system [24,25]. From this remote site, -according to Braak staging concept-, amyloid pathology spreads to the lower brainstem and further up to the forebrain [26,27].

Indeed, PD patients very often display GI dysbiosis [28–35]. Microbiome analysis of PD patients vs. healthy subjects revealed changes in relative abundance of certain bacterial genera rather than appearance or disappearance of a single species. For instance, the abundance of *Prevotella* was consistently reduced in fecal samples of PD patients as well as those of anti-inflammatory, butyrate-producing bacteria from the *Blautia*, *Coprococcus*, and *Roseburia* genera [28]. By contrast, several studies reported an increase in the relative abundance of genus *Lactobacillus*, *Bifidobacterium*, *Ralstonia* and *Akkermansia* in PD [31,36,37]. It is also worth noting that colonization of αSyn overexpressing mice with fecal microbiota from PD patients enhances motor symptoms compared to microbiome transplants from healthy humans [38].

Among the factors, influencing the gut microbiome, antibiotic exposure has profound and sometimes persisting impact on the bacterial composition, diversity and function of the intestinal flora [39]. In addition to the use antibiotics for medical reasons, the human body is unintentionally exposed to antibiotics present in feeds and in the environment. Prior to 2017, 80% of all antibiotics were given as feed additives to the livestock, in the United States. https://www.ncbi.nlm.nih.gov/books/NBK216502/. Animal husbandry use subtherapeutic dose of different antibiotics to increase the growth rate and feed efficiency, as well as for disease prevention in overcrowded locations including aquacultures [40–42].

Antibiotics decrease the microbial diversity of the gut flora, modulate *Bacteroidetes/Firmicutes* ratio and result in overgrowth of opportunistic pathogens [43,44]. For instance, a 7-day treatment with commonly used antibiotic groups: fluoroquinolones and β-lactams, significantly decreased microbial diversity by 25% and reduced the core phylogenetic microbiota from 29 to 12 taxa [45,46]. Another recent study on healthy subjects, found an immediate bloom of *Enterobacteria* and other pathobionts along with significant depletion of *Bifidobacteria* and butyrate-producing species in response to a meropenem, gentamicin and vancomycin cocktail. Although the microbiome of the subjects recovered to near-baseline composition within 1.5 months, some common species, which were present in all subjects before the treatment, remained undetectable after 4 months [47].

Table 1
Comparison of antibiotic consumption data from the ESAC project and prevalence of Parkinson's disease (PD) in 29 European countries.

Country	J01 DID (100%)	J01C %	J01D %	J01F %	J01M %	J01A %			% Change of PD prevalence 1990–2016
							J01CE + CF %	J01CA + CR %	
Austria	***13.42***	39.86	11.92	21.84	9.83	9.16	8.56	31.44	14.2
Belgium	***25.1***	45.05	12.35	11.31	9.4	10.99	1.63	42.31	12.4
Bulgaria	***19.27***	44.83	9.7	6.95	7.73	14.63	7.73	37.2	0.8
Cyprus	***33.25***	45.95	19.54	10.64	12.09	8.42	0.45	45.53	16.3
Czech	***17.22***	42.21	5.63	16.02	6.79	15.91	12.95	29.26	9.3
Denmark	***13.9***	62.01	0.25	1.58	2.15	8.56	41.87	20.7	45.9
Estonia	***11.86***	38.95	6.07	13.49	6.4	20.4	2.6	36.25	1.5
Finland	***18.34***	30.86	12.43	9.16	4.36	22.84	10.3	20.55	5.8
France	***30.63***	50.89	12.04	13.22	6.75	10.67	2.25	48.64	−2.2
Germany	***13.69***	32.06	9.42	15.7	8.32	22.71	10.29	21.76	11.5
Greece	***33.46***	33.17	21.63	25.04	8.36	7.74	2.36	30.81	13.7
Hungary	***18.05***	44.48	12.57	14.68	8.08	10.69	5.48	39	9.5
Iceland	***20.95***	50.88	2	7.54	3.19	24.24	19.76	31.12	13.4
Ireland	***19.8***	49.64	4.89	14.74	3.88	16.51	8.53	41.11	17.2
Italy	***26.04***	48.77	7.29	19.05	12.01	1.88	0.15	48.61	−3.4
Latvia	***11.52***	45.92	1.56	7.81	8.42	20.39	1.38	44.53	7.6
Lithuania	***22.9***	56.85	7.77	7.29	5.54	9.3	15.81	41.04	8.8
Luxembourg	***27.06***	40.68	18.36	14.07	8.9	9.75	1.25	39.76	13.4
Malta	***20.1***	44.47	22.13	16.81	8.5	5.22	0.59	43.93	15.4
Netherlands	***10.3***	39.02	0.67	12.33	8.34	23.88	7.28	31.74	−7.5
Norway	***15.57***	42.58	1.34	10.85	2.69	18.81	28.83	13.68	87.1
Poland	***21.69***	43.56	10.14	11.2	5.16	15.39	3.04	40.57	14.2
Portugal	***23.93***	48.34	12.53	1.37	13.16	5.22	2.84	45.5	31.9
Romania	***10.2***	42.25	24.21	17.94	12.35	1.07	2.94	39.31	10.2
Slovakia	***25.34***	51.77	11.68	16.33	6.62	7.97	16.33	35.39	9.7
Slovenia	***16.8***	59.52	3.75	17.32	8.21	3.86	9.9	44.58	9.7
Spain	***19.35***	57.31	10.49	13.33	11.67	3.25	1.8	55.45	8
Sweden	***15.05***	47.3	2.99	3.98	19.4	21.26	37	10.36	13.6
UK	***15.64***	45.84	5.11	15.34	3.08	21.73	9.78	36.06	22.3
Pearson R	**−0.097**	**0.118**	**−0.195**	**−0.262**	**−0.305**	**0.032**	**0.537**	**−0.446**	
Pearson *p*	***0.795***	0.330	0.110	0.239	0.087	0.375	***0.002***	***0.022***	

Antibiotic classes are labeled according to the ATC code (https://www.atccode.com/).
J01-all antimicrobial drugs; J01C- Penicillins; J01D- β-lactam antibiotics; J01F- Macrolides, lincosamides and streptogramins; J01M- Quinolone antibacterials; J01A- Tetracyclines; J01CE + CF- β-lactamase sensitive + resistant penicillins; J01CA + CR- Extended spectrum of penicillins and combinations of penicillin including β-lactamase inhibitors. DID: Defined Daily Dose (DDD)/1000 Inhabitants/Day. ESAC project: European Surveillance of Antimicrobial Consumption (1997–2010).

Further deleterious effects of antibiotic treatment are induction of bacterial biofilm formation by *E. coli* [48] and (2) producing low grade systemic inflammation by compromising gut barrier function, luminal signaling and metabolism [44]

The hypothesis

We hypothesize that exposure to certain antibiotics are involved in the pathogenesis of PD. Based on the data listed above, it is likely that certain antibiotics change the gut microbiome favoring *curli*-producing species. These bacteria deposit αSyn in the enteric nervous system (ENS) and promote further amyloid deposition via cross-seeding, which results in formation of transmissible self-propagating prion-like proteins. Amyloidosis appears in the ENS and later on in the central nervous system until the full expression of motor symptoms of PD develops, due to the loss of dopamine supply in basal ganglia. In addition, antibiotics result in a low-grade systemic inflammation, which also contributes to damage of neurons in enteric and central nervous system.

Evaluation of the hypothesis

We tested the hypothesis whether consumption of different groups of antibiotics, belonging to four major groups (penicillin /J01C/, cephalosporin/J01D/, quinolones/J01M/, macrolides/J01F/) is associated with the change of PD prevalence in different European countries [4].

Antibiotic consumption data, collected between 1997 and 2009 by the ESAC project (European Surveillance of Antibiotic Consumption network; Table 1) and data from the ECDC (European Centre for Disease Prevention and Control) database (2010–2017; Table 2) were used.

Within the penicillin group, consumption data of narrow spectrum penicillins (J01CE) plus penicillinase resistant penicillins (J01CF) and the extended spectrum penicillins (J01CA) plus β lactamase inhibitor combination penicillins (J01CR) were separately compared to PD prevalence change data.

Changes in PD prevalence between 1990 and 2016 were obtained from [4]. During this period, there was a 2.5x increase of patients diagnosed with PD. It should be noted, however, that the increase of PD prevalence was not solely due to increasing number of older people, because age-standardized prevalence rates were also increased. However, there is a possibility that higher number of cases were diagnosed due to increased awareness of medical facilities.

Correlation was calculated between antimicrobial consumption data and changes in PD prevalence. Significant positive correlation *($r = 0.537$, $p = 0.002$)* was found between the consumption of narrow spectrum + penicillinase resistant penicillin (J01CE + CF) and the increased prevalence of PD (Fig. 2, Table 1). No positive correlation was found between the other groups of antibiotics (J01D, J01M, J01F) and the joint group of penicillin compounds (J01C) featured in the ESAC project and the ECDC antibiotic consumption data. By contrast, we found a significant negative correlation between consumption of broad spectrum penicillin (J01CA) + combination penicillin (J01CR) and PD prevalence. This phenomenon might be explained by the fact that some antibiotics might have an anti-neuroinflammatory action, which is beneficial in PD.

Although a statistically significant correlation has been found between increasing prevalence of PD and exposure of penicillin antibiotics

Table 2
Comparison of antibiotic consumption data from ECDC project and prevalence of Parkinson's disease (PD) in 30 European countries.

Country	J01 DID (100%)	J01C %	J01D %	J01F %	J01M %	J01A %	J01CE %	J01CR %	%Change of PD prevalence 1990–2016
Austria	***12.55***	38.13	11.33	25.24	9.23	7.28	6.55	25.8	14.2
Belgium	***22.75***	45.78	5.7	14.8	11.25	7.23	0.15	22.61	12.4
Bulgaria	***17.52***	31.1	15.88	20.27	14.58	7.67	1.23	11.36	0.8
Croatia	***17.4***	43.51	15.1	16.63	10.38	5.18	4.06	21.83	7.9
Cyprus (a)	***26.02***	35.38	18.65	11.07	18.64	10.97	0.33	24.59	16.3
Czech	***16.59***	35.64	8.9	22.2	5.99	11.47	11.28	16.83	9.3
Denmark	***15.49***	63.02	0.18	12.98	3.1	10.4	28.99	4.96	45.9
Estonia	***10.28***	29.92	9.24	23.05	7.85	14.09	1.92	12.3	1.5
Finland	***16.44***	29.81	12.02	7.46	4.94	22.77	7.73	5.4	5.8
France	***23.55***	51.52	8.46	14.34	2.3	10.05	0.89	20	−2.2
Germany	***13.29***	24.85	19.38	18.22	10.2	15.24	5.77	2.41	11.5
Greece	***30.86***	29.87	22.48	25.16	8.21	6.53	0.28	15.36	13.7
Hungary	***13.65***	33.94	12.68	21.62	16.37	7.23	2.19	24.9	9.5
Iceland	***18.8***	48.55	2.84	8.71	5.13	22.28	11.56	15.69	13.4
Ireland	***19.58***	48.32	5.55	24.05	4.47	11.84	5.26	21.77	17.2
Italy	***22.22***	45.87	9.01	18.5	14.93	1.98	0.1	33.46	−3.4
Latvia	***10.98***	38.4	4.96	14.7	9.27	17.34	0.45	11.15	7.6
Lithuania	***14.01***	46.92	7.36	13.4	6.94	8.8	1.65	21.52	8.8
Luxembourg	***22.31***	37.64	14.01	18.13	11.9	6.38	0.14	24.07	13.4
Malta	***19.46***	32.77	21.43	19.66	12.01	5.48	0.4	25.56	15.4
Netherlands	***9.61***	32.41	0.34	14.73	8.19	21.56	3.02	23.63	−7.5
Norway	***15.51***	39.53	0.55	9.93	3.08	19.11	21.65	0.1	87.1
Poland	***20.47***	32.85	11.99	19.49	6.32	9.99	1.04	14.8	14.2
Portugal	***17.56***	47.16	8.06	16.55	12.49	3.76	0.14	34.85	31.9
Romania (a)	***26.11***	47.78	14.79	11.63	13.55	3.06	3.31	22.51	10.2
Slovakia	***20.15***	30.41	19.03	28.03	9.81	7.05	6.34	18.56	9.7
Slovenia	***11.53***	60.89	5.39	16.54	9.64	2.47	15.02	24.8	9.7
Spain (b)	***18.72***	54.72	8.3	12.25	13.87	3.57	0.45	32.3	8
Sweden	***12.66***	49.81	1.07	4.83	5.58	17.75	27.56	7.47	13.6
UK	***17.48***	38.23	1.81	17.14	2.59	23.8	4.69	4.62	22.3
Pearson R	−0.015	0.182	−0.296	−0.220	−0.318	0.167	0.549	−0.389	
Pearson *p*	*0.485*	*0.538*	*0.796*	*0.177*	*0.086*	*0.821*	***0.002***	***0.012***	

Antibiotic classes are labeled according to the ATC code (https://www.atccode.com/).
J01-all antimicrobial drugs; J01C- Penicillins; J01D- β-lactam antibiotics; J01F- Macrolides, lincosamides and streptogramins; J01M- Quinolone antibacterials; J01A- Tetracyclines; J01CE- β-lactamase sensitive penicillins; J01CR- Combinations of penicillin including β-lactamase inhibitors. DID: Defined Daily Dose (DDD)/1000 Inhabitants/Day. ECDC project: European Centre for Disease Prevention and Control (2010–2017).

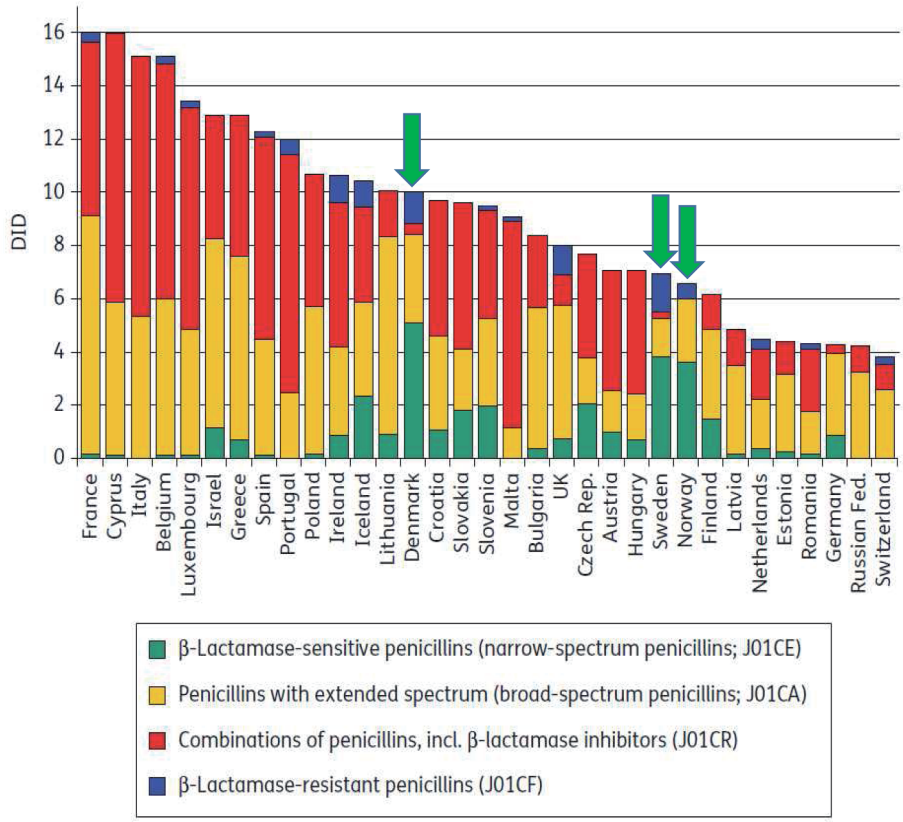

Fig. 1. Chart indicating penicillin consumption in different European Union (EU) countries (ESAC project). Penicillin consumption is expressed in DID. DID is the Defined Daily Dose (DDD)/1000 Inhabitants/Day. Countries marked with green arrows consume the highest amount of narrow spectrum penicillin (green) and β-lactamase resistant penicillin (blue) within their respective column (total consumption). Data were obtained from ESAC-Net interactive database: https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in different European countries, it should be confirmed by preclinical studies and detailed retrospective analysis of antibiotic exposure data of PD patients. The geographical distribution of the correlation is also worth of mentioning. While the correlation was strong in the Scandinavian countries (Denmark, Sweden and Norway), it is also interesting to note, that PD prevalence decreased in Holland, France, Italy, Israel, countries with low-to-average J01CE + J01CF exposure. Another confounding factor would be that the consumption data are the sum of antimicrobials used in the community (primary care sector) and in the hospital sector. Secondary consumption data are not included.

Consequences of the hypothesis and discussion

There is a general agreement in the literature that, apart from genetic background, PD is caused by some external effect and the primary change leading to the disease is the modified gut flora, dysbiosis. Even the suspected toxic agents, like pesticides, operate through the altered microbiome in the process of developing PD. Thus, as mounting evidence supports a role for the microbiota in the regulation of human behavior and neuronal functions, concerns arise about possible detrimental interactions with the commensals and its consequences in terms of the development of neurological disorders. Considering the fact that antibiotics are powerful agents influencing the microbiome, it is likely that some penicillins, as “external factors” initiate gut dysbiosis, which contribute to the development of PD. Our study compared global antibiotic consumption to the change of PD prevalence in different European countries in the past 25 years might provide some clues elucidating the issue [4]. To support our hypothesis, a recent work evaluated the impact of antibiotic exposure on the risk of PD in a register-based case-control study in Finland. This study also found significant association between exposure to certain types of oral antibiotics and increased risk of PD, with a delay that is consistent with the proposed duration of a prodromal period [49].

Our findings shows connection between high consumption of narrow spectrum penicillin and the highest prevalence change of PD without any other significant positive correlation from the comparisons of antibiotic consumption databases and PD prevalence. The countries (arrows) with the highest prevalence increase of PD, really “pulling up” the diagram, featuring the highest consumption of narrow spectrum penicillin between 1997 and 2009 (ESAC project) (Fig. 1).

Two major mechanisms may underlie the connection between exposure of certain antibiotics and increased prevalence of PD.

1. Antibiotics induce gut dysbiosis, a microbial imbalance, in which certain curly-producing bacteria gain abundance in the microbiome. Curly, as a functional αSyn, excreted to the extracellular space and exaggerates additional amyloid deposition. The αSyn pathology has the ability to spread from the gastrointestinal tract to the brain and results in loss of vulnerable dopamine synthesizing neurons in the substantia nigra.

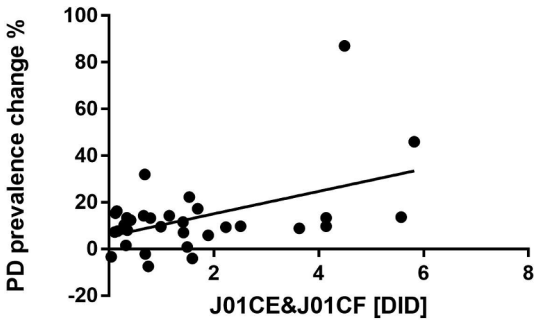

Fig. 2. Correlation between consumption of certain penicillins and prevalence of Parkinson’s disease. Consumption of narrow spectrum β-lactamase sensitive (J01CE) and β-lactamase resistant penicillins is expressed in DID (DID = Defined Daily Dose (DDD)/1000 Inhabitants/Day).

2. These antibiotics may promote inflammation, via translocation of live gut bacteria and inhibition of anti-inflammatory, short chain fatty acid (SCFA) (butyrate)-producing bacteria. Systemic inflammation in general-, and local neuroinflammation (microglia activation), in special-, contribute to PD pathogenesis.

These mechanisms are not mutually exclusive. For better understanding the relationship between antibiotics – microbiome – and PD, preclinical experiments and retrospective human studies should be designed. If our hypothesis is correct, a symbiotic (application of pre + pro biotics) strategy to fight PD, might be elaborated Fig. 2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109564.

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