REVIEW

# Bacteriophages: co-evolving with bacteria to provide useful traits

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ABSTRACT

Bacteriophages are viruses that infect and kill bacteria. Being the most abundant biological entity, bacteriophages show enormous diversity and evolutional patterns in nature. Phage comparative genome analysis has revealed the existence of genetic mosaicism among tailed phages with different segments having distinct evolutionary histories. Phages undergo either lytic or lysogenic cycle; in lysogeny, phage DNA is integrated into the bacterial genome, which is then propagated along. As in any other host- pathogen system, both the phage and its bacterial host co-evolve with each other, and it is well documented that this mechanism provides many beneficial traits to bacteria, like enhanced fitness, ability to fight with pathogens, etc. This review highlights the advances in understanding the evolutionary patterns of bacteriophages and how they co-evolve with their bacterial hosts to provide useful traits, particularly in controlling plant pathogenic bacteria.

KEYWORDS: Bacteria; Bacteriophage; Phage-bacteria interaction

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## INTRODUCTION

Bacteriophages or phages are viruses which can infect and kill bacteria. With more than 1031 phage particles, phages are considered as the most abundant biological entity in the environment (Brüssow and Hendrix 2002; Hatfull 2008). Fredrick Twort and Felix d'Herelle in 1917 were the first to discover bacteriophages. Prior to them attempts at identifying similar antibacterial agents had been made, but they were the first to confirm the agents to be of viral origin. Apart from enormous morphological diversity, bacteriophages show varied nucleic acid composition, diverse origin and unique patterns of evolution. Their diversity is so enormous that the size of the genome may vary from 4 kb to 600 kb as in the case of mycobacteriophage (Brüssow and Hendrix 2002). With advancement in next generation sequencing, the number of sequenced bacteriophage genome are increasing day by day, of which majorly are double stranded DNA tailed phages of the order Caudovirales (Ackermann 2007).

In general, the transmission of bacteriophages leads to lysis or death of the infected bacterium marking the ending of lytic cycle. Some bacteriophages termed as temperate phages or prophages remain integrated into the genome of the bacteria to enter into the lysogenic cycle. Upon sensing favourable conditions, the prophage switches to lytic state from the dormant lysogenic state to carry out its propagation. In order to remain in lysogenic state, prophages express genes for repressing the lytic cycle (Ptashne 1992). Apart from essential genes, prophages also carry some additional genes, which provide advantage to the bacterial hosts that harbor them. Certain prophages harbour cargo genes which may be coding for traits required to adapting in the bacterial host, such as virulence factors or toxins in pathogenic bacteria (Ohnishi et al. 2001; Banks et al. 2002; Boyd and Brussow 2002; Brussow et al. 2004; Thomson et al. 2004). As most prophages lyse bacterial cell upon lytic cycle induction, a balance between the lytic cycle induction and lysogeny is the key, which has subsequent impacts in the phage-bacteria interaction. Understanding the evolutionary mechanisms in bacteriophages and the way they integrate themselves to propagate along with bacterial genomes is essential to get an insight about this balance. Vertical evolution in bacteria involving gene duplication, mutation, gene disruption cannot be always possible, particularly when a varied gene combination is necessary for adapting to a changing environment. On the other hand, horizontal gene transfer such as uptake of foreign DNA, conjugation, phage transduction can readily serve the combinatorial gene constellations required for survival in the changing environment. In this review, the impact of bacteriophages in such processes is discussed, acknowledging the fact that the evolution of prophages and their hosts is very closely linked and understanding phage evolution may also help us ascertain the influence of prophages in bacterial fitness and evolution. Thus, this review is a deliberate attempt to understand the process of evolution of bacteriophages as well as their hosts and how this can be utilized in controlling important plant pathogens and diseases.

### Genome evolution in bacteriophages

Among several evolutionary theories, the modular theory of evolution in phage is well accepted. The modular theory states that the outcome after evolution does not result into a given virus rather a collection of interchangeable genetic materials and modules capable of performing specific biological function (Susskind and Botstein 1978; Susskind 1980). Each virus in nature is a favourable combination of these modules selected in the course of evolution to work optimally in a niche. Susskind & Botstein (1978) proposed that mosaic relatedness in the phage genomes is a result of genetic switch of such modules by either site specific or homologous recombination at definite 'linker' sequences present in between the genes.

Though there are some reports supporting these linker sequences, this model does not explain other exchange events which may be equally important (Hatfull 2008).

From the phage comparative genome analysis, the existence of genetic mosaicism is well noted among tailed phages with different segments having distinct evolutionary histories (Brüssow and Desiere 2001; Brüssow and Hendrix 2002). These days with increasing knowledge of phage genomes, the modular theory is modified to explain the occurrence of mosaic boundaries at random genomic locations which might be as a result of non-homologous or illegitimate recombination. However, most of these recombinations are disadvantageous, leading to natural selection and elimination of the population (Juhala et al. 2000; Brüssow and Hendrix 2002). It has been found that in the surviving population, majority of the mosaic boundaries lies at gene boundaries or at boundaries within protein domains (Juhala et al. 2000; Lawrence et al. 2002). More recently it has been shown that bacteriophages evolution takes up within two general evolutionary modes viz. low and high gene flux modes. The lytic phages undergo low gene flux mode only and temperate phages evolve into high as well as low gene flux modes wherein, these evolutionary modes are a function of genomic constitution of the phages along with their bacterial host and lifestyle (Mavrich and Hatfull 2017).

## Role of 'morons' in the bacteriophage genome

Certain phages may take up new genes by accumulation of 'moron' in the genome (Juhala et al. 2000). These additional genetic materials termed as 'morons' are found in a phage but not in related phages, which might be a result of insertion in between genes of any ancestral phage. A moron element, gp15 encoded by the temperate phage HK97 was found within the morphogenesis region of the phage tail and was not present in most of the closely related phages (Cumby et al. 2012). Typically moron is an open reading frame with a flanking promoter and terminator, which lets it to predict that they are part of repressed prophage and are expressed from that phage during its lytic phase (Juhala et al. 2000). Phages may acquire ecologically important genes as morons for adapting to new environment (Breitbart and Rohwer 2005). Morons present in temperate phages may also confer beneficial functions to the bacterial host (Brüssow and Hendrix 2002). For instance, the moron element containing lom and bor genes expressed in λ prophage of *E. coli* increases the adherence to host cells, and also renders enhanced survival of the pathogen in the serum (Barondess and Beckwfth 1990; Vica et al. 1997). The actively expressed moron element, gp15 of the prophage HK97 was found to provide resistance to the host against phages HK97 and HK75 infection (Cumby et al. 2012). Besides this, maintaining genetic diversity in phage genomes by homologous and non-homologous recombination, insertion, deletions and point mutations may influence the life cycle of phages along with specificity towards their host (Lucchini et al. 1999; Desiere et al. 2002).

Certain catalytic RNAs like Group I introns are capable of self-splicing (Cech 1990) and can shape the genome dynamics in microbes leading to diversification in microbial genomes (Haugen et al. 2005) . Some phages that infect lactic acid bacteria (LAB) occasionally harbours Group I introns in their genomes; sometimes introns have also been found within late-transcribed genes of the phage such as head, tail, endolysin, and terminase large subunit (Brüssow and Desiere 2001). These Group I introns are also capable of invading new genomic sites, facilitated by proteins encoded by the introns (Haugen et al. 2005). In the recent years, evolution in phage genomes has been well studied by comparative genomics studies with phage genome sequences. As the phage DNA is also replicated alongside host

bacterial DNA, phages, per se, can undergo horizontal gene transfer with host bacterial chromosomal DNA, plasmid DNA and other co-infecting phages. Metagenomic studies can reveal the abundance and genomic diversity of phages in an environment which can be utilised in establishing the evolutionary relationship of the phages with their hosts (Edwards and Rohwer 2005).

## Bacterial genome evolution

Bacteria can evolve by genetic exchange, competition and selection among themselves. The rate of mutation in bacteria generally ranges from 10-6 to 10-9 per nucleotide per generation. In the course of evolution, it could be possible that phages may have taken part and constituted the virulence factors in contemporary bacterial pathogens. Moreover, like any other living entity, genetic exchange, gene disruptions and deletions occur frequently in bacterial genome for better adaptability to a constantly changing environment. As bacteria lack sexual cycles, exchange of alleles within a population is not possible. Instead, in bacteria horizontal gene transfer takes place, where entire gene can be incorporated into the genome from varied sources. The size of the horizontally transferred DNA can range from a few kb to more than 100 kb which can code for different functions. Bacteria can uptake these genes as a naked piece of DNA and carry them in the form of extra chromosomal plasmid DNA, conjugative transposons, or as prophages.

## Co-evolution between phages and bacteria

Co-evolution between ecologically interacting species results as a dynamic course of adaptation and counter-adaptation (Janzen 1980). When it comes to bacteriophages and their bacterial hosts, evidences suggest that these two populations are co-evolving rapidly over time. Phages being more in number in nature put bacteria under constant threat. To counter this threat, bacteria have evolved various strategies viz. blocking entry of the phage DNA, restriction-based modification in the infecting phage DNA, CRISPR/Cas (Clustered Regularly Interspersed Palindromic Repeats) mediated defence mechanism. To overcome these barriers, phages in counter-defense evolve along with their bacterial hosts. For instance, bacteria that have lost or undergone modification in the receptors for phage entry might be infected by phages with modified binding sites. As in case of Bordetella spp. which can undergo phase variation from virulent Bvg+ phase to nonvirulent Bvg– phase for cell surface alteration and colonization in host, where only Bvg+ phase expresses pertactin autotransporter (Prn), a phage entry receptor (Uhl and Miller 1996; Liu et al. 2002). Notably, the Bordetella phage BPP-1 can still infect Bvg– phase lacking the phage entry receptor indicating that this phase variant has evolved to counter the lack of its primary entry receptor (Labrie et al. 2010). In order to combat the restriction modification systems of bacteria, some phages have acquired methyltransferase genes which can alter the restriction recognition sites. Certain bacteriophages have adapted the strategy of recombination of the proto-spacer sequence which is recognized by the RNA transcript of the host, to counter the CRISPR/Cas system of the bacterial hosts. Recently, a co-evolution experiment with Streptococcus thermophilus and phage 2972 revealed that CRISPR immunity facilitates fixation of SNPs (single nucleotide polymorphisms) which specifically aggregates at the genomic sites of phage which is targeted by CRISPR (Paez-Espino et al. 2015). This antagonistic co-evolution in natural populations leading to the coexistence of phage with its bacterial host is very important for shaping genetic diversification between populations (Buckling and Rainey 2002).

Prophages may contribute around 10–20% of bacterial genome leading to mutually beneficial genomic evolution between phage and bacterium (Casjens 2003; Edwards and Rohwer 2005). In Lactic Acid Bacteria, around ~7.4% of the bacterial chromosomal DNA may have originated from

prophage sequences (Bolotin et al. 2001), that may in turn account to significant genomic differences among strains (Wegmann et al. 2007). Prophages are also reported to have role in horizontal gene transfer, which greatly influences in shaping the physiology, diversity and evolution in bacteria (Casjens 2003). It is also reported that temperate phages can confer additional selective advantage to the host to balance the additional metabolic load on the bacterial host (Brüssow and Hendrix 2002). Also, the lysogenic conversion genes encoded by the prophage might confer immunity and protect the bacterial host from subsequent infection (Canchaya et al. 2003). However in certain cases like CTX cholera, shiga, botulinum and diphtheria toxins, lysogenic conversion genes might add to the virulence factor of the host bacteria (Waldor and Mekalanos 1996; Skurnik and Strauch 2006). One key aspect in understanding prophage-bacterial relationship is to identify and characterize the prophage elements embedded in the bacterial genome. Ronning et. al. (2010) identified and categorised 37 prophages, putative prophages and prophage-like elements in various Burkholderia species and the strategy used by them is represented in a flow diagram (Figure 1).

## Potentiality of phages as bio-control agents

Since their discovery, the utility of bacteriophages as anti-bacterials have been recognized and several attempts have been made both in the field of animal and plant sciences to characterize them. In 1919, d'Herelle used preparations of phages for treating patients suffering from dysentery (Wilkinson 2001). Attempts at using phages to treat human diseases like cholera, staphylococcus infection, and bubonic plague were also successful (Sulakvelidze et al. 2001). Mallmann and Hemstreet in the 1920s were able to inhibit Xanthomonas campestris pv. Campestris, the "cabbage- rot organism" using filtrate from decomposing cabbage. However, this pre-antibiotic era 'bacteriophage therapy' soon was overlooked with the eventful discovery of antibiotics. But recently, with the development of antibiotic resistant microbes, the prospects of using phage therapy is getting popularized and several human and plant diseases have been controlled ( Jun et al. 2014; Rombouts et al. 2016; Yen et al. 2017) . The most striking advantage of phages being used in controlling plant diseases are due to their specificity to the pathogen. Having a narrow host range, phages can be used as phage mixtures for targeting bacterial species within a given genus only (Basit et al. 1992). So, that makes the use of phages more desirable over chemical pesticides that non-selectively kill bacteria including the beneficial ones. Also, unlike pesticides, phages are present in nature and hence human exposure towards them is very common.

## Phage in controlling plant pathogens

Recently, much advancement has been made in the usage of phage as bio-control agent against some economically important bacterial pathogens of plants which is listed are Table 1. The decisive factor if a phage can be utilized as bio-control agent or not depends on its property of being a temperate phage or an exclusively virulent lytic phage. In temperate phages, the phage genome is incorporated in the genome of bacteria and replicates until any trigger induces it to switch in to lytic cycle. The triggers can be various physical factors like UV radiation, heat and chemical in nature. Many studies have suggested that certain plant extracts also has the potential to induce bacterial lysogens. Studies conducted in early 90s by Gvozdyak have suggested that plants can induce lysogens, a strategy that plants could exploit to eliminate bacterial pathogens e.g. the phage Erwinia amylovora influences the occurrence and severity of fire-blight disease. Similarly, Sato has shown that mulberry leaves extracts could induce lysogens of Pseudomonas syringae. Moreover, prophage genes can also add to the fitness of the bacterial host. The prophages ECA41 and ECA29 of the plant pathogenic bacteria Pseudomonas atrosepticum help in the motility of the bacteria (Evans et al. 2010). Prophages can

harbour genes for production of toxins e.g. shiga, cholera and diphtheria toxins (Abedon and LeJeune 2005). In a recent study, it has been shown that even fungal pathogens like Rhizoctonia solani, which causes sheath blight disease in rice can be controlled by a prophage tail like protein derived from Burkholderia gladioli NGJ1 (Swain et al. 2017)

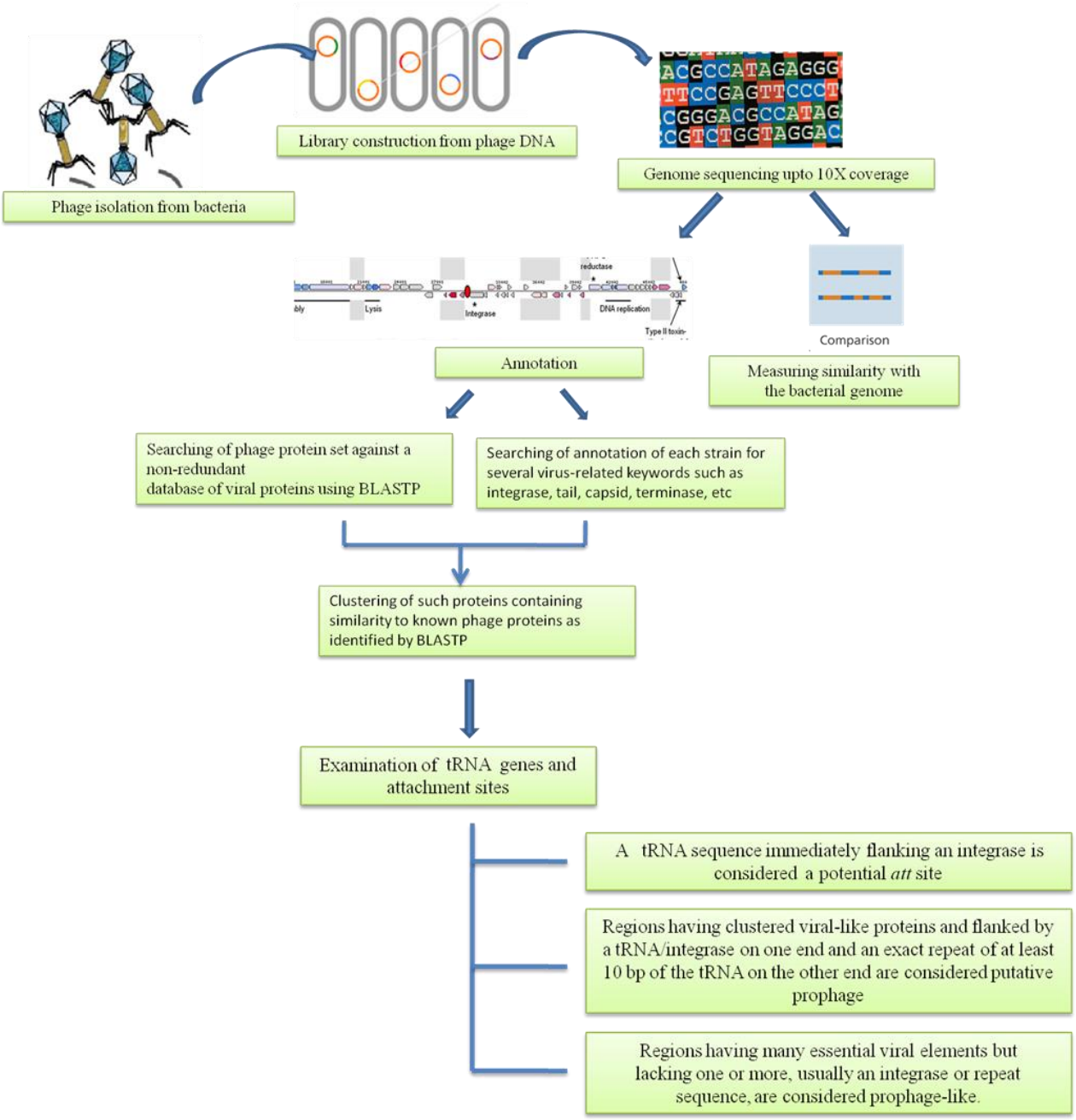


Figure 1. Strategy used for identification of putative prophages and prophage-like elements in bacterial genome (Ronning et al. 2010).

Table 1: Listing of some of the bacteriophages used as bio-control in controlling plant pathogens

| Disease | Pathogen | Host | Phage used in study |
|---|---|---|---|
| Soft rot | *Dickeya solani* | Potato | ØD1, ØD2, ØD3, ØD4, ØD5, ØD7, ØD9, ØD10, ØD11 (Czajkowski et al. 2014) |
| Common scab | *Streptomyces scabies* | Potato | ØAS1 (McKenna et al. 2001) |
| Bacterial wilt | *Ralstonia solanacearum* | Tomato | ØRLS1 (Fujiwara et al. 2011) |
| Bacterial wilt | *Ralstonia solanacearum* | Tomato | phage PE204 (Fujiwara et al. 2011) |
| Bacterial spot | *Xnathomonas campestriespv. vesicatoria* | Tomato | Formulated phage cocktails (Bae et al. 2012) |
| Pierce's disease | *Xylella fastidiosa* | Grapevines | Phage cocktail of Sano, Salvo, Prado and Paz (Das et al. 2015) |
| Soft rot | *Pectobacterium carotovorum ssp. carotovorum* | Lettuce | Phage PP1 Lim et al., 2013 |
| Common scab | *Streptomyces scabies* | Radish | Phages Stsc1, Stsc3 (Goyer 2005) |
| Bacterial blight | *Pseudomonas syringae pv. porri* | Leek | phages vB_PsyM_KIL1, vB_PsyM_KIL2, vB_PsyM_KIL3, and vB_PsyM_KIL3b (Rombouts et al. 2016) |
| Fire blight | *Erwinia amylovora* | Pear | ØEa1337-26, ØEa 2345 (Boulé et al. 2011) |
| Bacterial spot | *Xanthomonas campestris pv. vesicatoria* | Tomato | Combination of phage and plant activator Obradovic et al., 2004 |
| Soft rot | *Pectobacterium carotovorums sp. carotovorum, P. wasabiae* | Potato | ΦEC2, LIMEstone1, ΦD3, ΦD5, ΦPD10.3, ΦPD23.1, PP1, My1, PM1, PM2, ZF40 (Czajkowski 2015) |
| Asiatic citrus canker and citrus bacterial spot | *Xanthomonas axonopodis pathovars citri* and *citrumelo* | Citrus | CP2, ΦXac2005-1, ccΦ7, ccΦ13, ΦXacm2004-4, ΦXacm2004-16, ΦX44 Xacm 47, ΦXaacA1 (Balogh et al. 2008) |
| Asiatic citrus canker disease | *Xanthomonas axonopodis pv. citri* | Citrus | XacF1 (Ahmad et al. 2014) |

| | | | |
|---|---|---|---|
| Soft rot | *Pectobacterium spp. and Dickeya spp.* | Potato | ΦPD10.3 and ΦPD23.1 (Czajkowski et al. 2015) |
| Potato bacterial wilt | *Ralstonia solanacearum* | Potato | P1 phage cocktail containing P-PSG-1, P-PSG-2, P-PSG-3, P-PSG-7, P-PSG-8, P-PSG-9 (Wei et al. 2017) |

## DISCUSSION

In this review, an attempt has been made to highlight the advances in understanding the evolutionary patterns of bacteriophages and how they are co-evolving with bacteria. This co-evolution between the phages and bacteria has enormously affected the fitness and diversity in bacterial populations and created an opportunity to use them in controlling plant pathogens. As phages interact with the bacterial microbiome and thus have an indirect influence on the plant host, it would be insightful to understand the rhizosphere virome and its impact on bacterial microbiome (Pratama et al., 2020). It is indeed surprising, that incorporation of prophages in the bacterial genome can result in strain difference in bacteria. It is worth mentioning that certain prophages which cannot excise from the bacterial host termed as 'grounded' prophages serve as an added advantage towards host genome evolution as well as acting as in horizontal gene transfer (Ramisetty and Sudhakari, 2019).

With the advancements in genomics, it is now a matter of flick to identify new prophages or phage-like elements buried in bacterial genome which can be utilized in plant pathology. However, the challenge is to correctly formulate the prophages and validate them in field trials. The major factors that need to be taken care of in phage cocktail formulations and their subsequent application are the stability of the formulation, time of application, impact on environment, cost and feasibility of bulk production along with constant monitoring over the effectively of the applied cocktail (Kering et al., 2019). Formulations of phage cocktails usually involve a right combination of multiple phylogenetically diverse phages which is thought to increase the treatment efficacy as well as relatively slows the evolution of bacterial resistance which is generally associated when treated with a single phage (Meaden and Koskella 2013). Although there is a potential risk of evolving bacterial resistance against phages, Meaden Sean and Britt Koskella proposed that a careful combination of antibiotic and phage treatments can mitigate the spread of antibiotic as well as phage resistance in the environment. A continuous check in the phage formulations and the bacterial pathogens is therefore required to combat the evolving phage resistant bacterial pathogens. Though phage therapy seems promising, amalgamation with the existing strategies can provide better means to control pathogens.

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The authors have declared to have no conflict of interest or competing interest.

## Authors' contributions

J.D. and G.J. conceptualized the idea and wrote the manuscript. The funders have no role in preparation of the manuscript or the decision to publish it.

## Declaration of originality

The authors declare that they have not copied text, figure or data from a particular source without appropriately citing it.

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