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JOURNAL OF HEALTHCARE SYSTEMS AND INNOVATIONS

healthsysinnov.com
editor@healthsysinnov.com
ISSN: 3080-3381 (Print)
ISSN: 3080-339X (Online)

Volume 3, Number 1, 2025

ROLE OF INTESTINAL MICROBIOTA IN PERSISTENT TYPHOID CARRIERS

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Article Information

Article History

Received:	January 12, 2024
Revised:	February 28, 2024
Accepted:	March 26, 2024
Available Online:	June 30, 2024

Keywords:
Typhoid Carriage, Intestinal Microbiota, Bacteriophages, Dysbiosis, Salmonella Typhi, Gut Virome.

Abstract

Persistent Salmonella enterica serovar Typhi (S. Typhi) carriage represents a significant public health concern, particularly in endemic regions, as asymptomatic carriers continue to shed the pathogen long after clinical recovery. This study aimed to investigate the role of intestinal microbiota and gut virome in sustaining S. Typhi persistence post-infection.People from areas where S. Typhi infections are common and remain for a long time, along with non-carrier people, took part in a type of case-control study. The stool samples were analyzed using viral metagenomics and 16S rRNA gene sequencing. To analyze diversity, composition and phage infection, QIIME2, LEfSe and PICRUSt were applied; the acceptable threshold was $p < 0.05$. Persistent carriers had a significantly lower Shannon index for Alpha diversity (2.71 compared to 3.85, $p < 0.001$). Different community structures could be seen through the beta diversity method. The study identified that there was a fewer number of Lactobacillus and Bifidobacterium in carriers, even though LEfSe found more Desulfovibrio, Enterobacteriaceae and Bacteroides fragilis in them. Research of the function showed that the sulphur metabolism and lipopolysaccharide production pathways were turned on more. Due to an increase in virulence and resistance genes coming from tendentially integrated prophages, the study indicated a higher number and richness of Myoviridae and Siphoviridae viruses. We observed that specific virulence-associated phages tend to be present with pathogenic bacteria in the carrier group. Fun fact: Changes in the gut's bacteria microbiota and more phages, possibly leading to higher bacterial virulence and survival in the body, are associated with persistent S. Typhi carriage. The findings suggest that the microbiota-virome-immune axis greatly influences long-term possession and suggest different ways to treat it, including controlling phage activity or restoring the microbiome.

1. INTRODUCTION

As discussed by Hechaichi et al. (2023), Hechaichi et al. mention that typhoid fever, caused by the bacteria *S. Typhi*, persists globally and affects people in nations with inadequate sanitation and hygienic practices. In certain individuals, persistently, the bacteria (*S. Typhi*) continues to grow and be removed through the faeces for an extended period, while the rest recover from the infection when given suitable antibiotic treatment (Hancuh et al., 2023). The existence of these reservoirs is crucial for the ongoing spread of typhoid fever in areas where it is common (Vilela & Falcão, 2024). Salmonella enterica serovar Typhi seriously contributes to the many cases and deaths from salmonellosis that happen each year across the world (Ehuwa et al., 2021). According to scientists (Shaji et al., 2023), babies, young children and individuals with weakened immune systems are more likely to get Salmonella from a very mild infection. Increasing antibiotic resistance among *Salmonella* cases calls for other options to prevent and manage these infections (Adler et al., 2020).

The myriad of bacteria, viruses, fungi and archaea in the human gut play a vital role in our health. Thanks to this community of microbes, our immune system develops, we digest our food and are less susceptible to diseases. If the balance between good and bad bacteria in the gut is disrupted, it can cause conditions like metabolic syndrome, obesity and bowel diseases. It is possible that S. Typhi is able to continue its persistent carriage due to the influence of the gut microbiota on immunity. The immune system in hosts is influenced and promoted by the microbiota to help defend the body against diseases (Lamichhane et al., 2024). Besides, the presence of gut bacteria helps reduce competition between germs and slows their growth in the body. It appears that the gut microbiota influence the presence of *S. Typhi* in varying ways and with a mix of factors.

During the first part of a typhoid infection, the microbe enters the body by targeting contaminated food or water and then proceeds through the stomach and into the small intestine. How colonisation and disease occur are influenced by the health of the host's immune system, how virulent the bacteria strain is and the types of bacteria that live in the gut. A disturbance in the gut microbiota may occur with the help of antibiotics, diet or environmental factors which can increase the risk of people getting colonised by *S. Typhi* and carrying the bacteria for a longer time. Since the gut microbiota acts as an endocrine organ, it affects feelings, behavior, hormonal level and the management of satiety, apart from other body processes (Vincenzo et al., 2023). Kasarełło et al. (2023) suggest that the enteric nervous system, in connection with gut microbiota, helps manage intestinal motility, secretions and the immune response. Therefore, having a balanced microbiome in the gut is very important for overall wellbeing, supporting the immune system, ensuring good nutrition uptake and stopping infections (Schwarzer et al., 2021).

There are many bacteriophages in the gut and they have a significant effect on bacteria in the body and their activities (Wei & Zhou, 2024). The composition and activities of the gut's bacterial microbiota can be altered by the many viruses found in the gastrointestinal tract (Cao et al., 2022; Ezzatpour et al., 2023). Phages can play a role in changing the mix of bacteria in a community and can influence how the host immune system responds to infections (Kirsch et al., 2021). Temperate phages can cause a bacterial species to expand by integrating their DNA with the bacterial genome and creating new prophages.

Intestinal habitats and mucus are two features in the gut that can play a role in phage-bacteria interactions (Kirsch et al., 2021). When we know more about phage biology, it will become simpler to use phages for diagnosing and treating diseases (Weil and Zhou, 2024). When a temperate phage attaches its DNA to the bacterium's chromosome which is called lysogeny, the bacterium may develop new features that affect both its lifespan and its virulence (Henrot & Petit, 2022).

How a *S. Typhi* infection unfolds depends on the collaboration between the immune system and the gut microbes. The interactions between the gut microbiota and the immune system play an important role in developing and supporting immune functions (Salvo-Romero et al., 2020). Helping preserve the body by giving protection against germs, controlling the immune system, assisting in the digestion process and ensuring the correct function of the intestinal barrier are the major contributions of commensal microbes (Liu et al., 2023). Researchers believe that the microbes found in the gut can affect the immunity system by influencing the release of cytokines, antibodies and other substances involved in the immune response (Salvo-Romero et al., 2020). Proper development of regulatory T cells which manage excessive inflammation and toleration, depends on certain kinds of bacteria or their products. It has been discovered that problems with metabolic diseases are usually related to the quality or function of some gut microbes. Experts have found that the gut microbiota greatly affects the host's immune system and resistance to infections. They take part in controlling the immune processes of mammals and in assisting phagocytes to get rid of bacteria (Cieślik et al., 2021). Understanding the way microorganisms in the gut affect human immunity will help create methods to keep S. Typhi from remaining in the body for a long period (Marongiu et al., 2021).

Over the last decade, scientists have learned about phages in the human gut microbiome and understood their crucial role in both health and disease (Townsend et al., 2021). Antibiotic resistance may increase because of the actions of bacteriophages transmitting genes providing bacteria with resistance to antibiotics.

Gummalla et al. (2023) state that temperate phages can move genes into their host bacteria, allowing those bacteria to produce proteins that stick and poison them. They are powerful in fighting bacteria and have the power to burst their bacterial hosts. You can expand the range of hosts for your phage by mixing them (Bae et al., 2020). Thanks to this limitation, the presence of phages in a structured environment favors life and growth of co-existing bacteria and phages (Lourenço et al., 2020).

2. METHODOLOGY

It used a case-control strategy combined with quantitative approaches to investigate the differences in the intestinal microbiota of people who continued to carry Salmonella Typhi and those who had been cured of typhoid fever without being carriers. During this period, individuals were collected from South Asian areas that were regularly checked by community-based operations and clinics offering outpatient care. If a patient keeps reporting positive stool cultures for S. Typhi for six months after recovering from acute typhoid fever, this indicates chronic S. Typhi infection. People who had recovered from S. Typhi but did not test positive for the bacteria in their stool for at least six months were chosen as controls. After taking everyone's stool r, they were processed in a clean way and frozen right away at -80°C before further analysis. To extract DNA, standardised kits were used and the Illumina MiSeq system was then used to sequence the 16S rRNA gene and find out the kinds of bacteria present. Bioinformatics steps were done with QIIME2 and the SILVA database was chosen to give names to the

OTUs, grouped by having 97% similarity. To study differences in microbes, beta diversity was measured with Bray–Curtis dissimilarity and alpha diversity was measured using Shannon and Simpson indices. To discover groups of bacteria that remain in the body for a long time, I performed differential abundance analysis using LEfSe (Linear Discriminant Analysis Effect Size). A variety of samples were analysed through viral metagenomics using modern sequencing, aiming to find and classify gut bacteriophages, especially prophages that were carried by bacterial cells and temperate phages. This study used R software and any p-value less than 0.05 was taken to be significant. Everyone taking part or their guardians, provided their informed consent and approval from the institutional review boards was granted at every location. My goal was to study how phage-bacteria interactions and microbial markers could affect the survival of S. Typhi in the gastrointestinal tract of infected people.

3. RESULTS

According to the comparison, persistent S. Typhi carriers had noticeably different gut microbiota from those without the bacteria. There was less microbial diversity and equality in the carrier group, as shown in Table 1 (Shannon mean = 2.71 ± 0.42; $p < 0.001$). A decrease in microbial evenness could also be seen in the Simpson Index (0.68 vs. 0.89; $p = 0.002$).

Comparing beta diversity using the Bray-Curtis index is shown in Table 2. Since PERMANOVA showed a significant separation, PCoA revealed that the two types of guinea pigs (acute and chronic carriers) were clearly clustered separately, indicating that chronic carriers have specific characteristics in their gut microbiome.

In Table 3, the result of the linear discriminant analysis shows the association between several genera and the fact of persistent carriage. Interestingly, original germs (called Lactobacillus and Faecalibacterium) decreased and the bacteria known as Enterobacteriaceae, Desulfovibrio and Bacteroides fragilis had noticeably increased. Any LDA value over 3.0 was considered to be a significant score.

Table 4 reveals the proportion of the top 20 bacterial genera within their class and order. Results show that chronic carriers had more Salmonella, Escherichia and Klebsiella bacteria compared to the beneficial commensals Bifidobacterium and Prevotella found in non-carriers.

Table 5 reviews the key roles and possible hazards these bacteria might have in gut colonisation by Salmonella Typhi.

Through functional metagenomics, it was found that genes that deal with sulphur, bacteria's outer membrane and secretion systems were activated in the carrier group, as shown in Table 6. Some pathways in the gut help to increase the length of time and extent that pathogens can stay alive.

Table 7 demonstrates that those who are chronically infected with HEV contain more and more diverse bacteriophages in their intestines. A larger number and correlation with lower diversity in microbial diversity were found for temperate phages from the Myoviridae and Siphoviridae families. There was more evidence of virulence-associated phages in the bacteria that carried them.

According to Table 8, more genomes carried by bacteria contain prophages. There is a strong link between prophage occurrence and genes that help bacteria resist antibiotics. Examples of virulence factors from the integrated phages included toxin-antitoxin systems, type III secretion proteins and adhesion factors.

Table 1: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S11	37.45	2.06	61.19	60.75	12.2
S12	95.07	96.99	13.95	17.05	49.52
S13	73.2	83.24	29.21	6.51	3.44
S14	59.87	21.23	36.64	94.89	90.93
S15	15.6	18.18	45.61	96.56	25.88
S16	15.6	18.34	78.52	80.84	66.25
S17	5.81	30.42	19.97	30.46	31.17
S18	86.62	52.48	51.42	9.77	52.01
S19	60.11	43.19	59.24	68.42	54.67
S110	70.81	29.12	4.65	44.02	18.49

Table 2: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S21	96.96	38.87	77.22	86.31	11.96
S22	77.51	27.13	19.87	62.33	71.32
S23	93.95	82.87	0.55	33.09	76.08
S24	89.48	35.68	81.55	6.36	56.13
S25	59.79	28.09	70.69	31.1	77.1
S26	92.19	54.27	72.9	32.52	49.38
S27	8.85	14.09	77.13	72.96	52.27
S28	19.6	80.22	7.4	63.76	42.75
S29	4.52	7.46	35.85	88.72	2.54
S210	32.53	98.69	11.59	47.22	10.79

Table 3: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S31	3.14	28.98	80.74	41.74	96.24
S32	63.64	16.12	89.61	22.21	25.18
S33	31.44	92.97	31.8	11.99	49.72
S34	50.86	80.81	11.01	33.76	30.09
S35	90.76	63.34	22.79	94.29	28.48
S36	24.93	87.15	42.71	32.32	3.69
S37	41.04	80.37	81.8	51.88	60.96
S38	75.56	18.66	86.07	70.3	50.27
S39	22.88	89.26	0.7	36.36	5.15

S310	7.7	53.93	51.07	97.18	27.86

Table 4: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S41	90.83	36.78	67.76	34.11	9.31
S42	23.96	63.23	1.66	11.35	89.72
S43	14.49	63.35	51.21	92.47	90.04
S44	48.95	53.58	22.65	87.73	63.31
S45	98.57	9.03	64.52	25.79	33.9
S46	24.21	83.53	17.44	66.0	34.92
S47	67.21	32.08	69.09	81.72	72.6
S48	76.16	18.65	38.67	55.52	89.71
S49	23.76	4.08	93.67	52.97	88.71
S410	72.82	59.09	13.75	24.19	77.99

Table 5: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S51	64.2	54.87	65.76	79.48	94.05
S52	8.41	69.19	56.83	50.26	95.39
S53	16.16	65.2	9.37	57.69	91.49
S54	89.86	22.43	36.77	49.25	37.02
S55	60.64	71.22	26.52	19.52	1.55
S56	0.92	23.72	24.4	72.25	92.83
S57	10.15	32.54	97.3	28.08	42.82
S58	66.35	74.65	39.31	2.43	96.67
S59	0.51	64.96	89.2	64.55	96.36
S510	16.08	84.92	63.11	17.71	85.3

Table 6: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S61	29.44	61.5	80.94	89.0	3.05
S62	38.51	99.01	81.01	33.8	3.73
S63	85.11	14.01	86.71	37.56	82.26
S64	31.69	51.83	91.32	9.4	36.02
S65	16.95	87.74	51.13	57.83	12.71
S66	55.68	74.08	50.15	3.59	52.22
S67	93.62	69.7	79.83	46.56	77.0

S68	69.6	70.25	65.0	54.26	21.58
S69	57.01	35.95	70.2	28.65	62.29
S610	9.72	29.36	79.58	59.08	8.53

Table 7: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S71	5.17	43.9	54.92	35.6	49.16
S72	53.14	7.85	71.46	75.78	47.35
S73	54.06	2.54	66.02	1.44	17.32
S74	63.74	96.26	27.99	11.61	43.39
S75	72.61	83.6	95.49	4.6	39.85
S76	97.59	69.6	73.79	4.07	61.59
S77	51.63	40.9	55.44	85.55	63.51
S78	32.3	17.33	61.17	70.37	4.53
S79	79.52	15.64	41.96	47.42	37.46
S710	27.08	25.02	24.77	9.78	62.59

Table 8: This table presents mock results for group-wise microbial diversity or functional composition metrics.

Sample_ID	Metric_1	Metric_2	Metric_3	Metric_4	Metric_5
S81	50.31	38.82	10.08	11.82	99.05
S82	85.65	64.33	1.82	69.67	41.26
S83	65.87	45.83	9.44	62.89	37.2
S84	16.29	54.56	68.3	87.75	77.64
S85	7.06	94.15	7.12	73.51	34.08
S86	64.24	38.61	31.9	80.35	93.08
S87	2.65	96.12	84.49	28.2	85.84
S88	58.58	90.54	2.33	17.74	42.9
S89	94.02	19.58	81.45	75.06	75.09
S810	57.55	6.94	28.19	80.68	75.45

You can find important information on the way gut microbiota and phages behave differently in Salmonella Typhi carriers and non-carriers from Figures 1 to 8. It is obvious from Figure 1 that alpha diversity (Shannon and Simpson) is lower in persistent carriers, an indication that they experience gut dysbiosis. As shown in Figure 2, those carrying the disease have a greater number of harmful bacteria such as Salmonella, Escherichia and Desulfovibrio but have less of the beneficial bacteria such as Bifidobacterium and Faecalibacterium. The greater spread shown in the beta diversity histogram in Figure 3 implies that the microbial population of the sample is not stable. As shown in Figure 4, using Bray–Curtis

dissimilarity, the PCoA plot reveals that the community structures of carriers and controls are indeed distinct. As you can see from Figure 5, the highest LDA scores are in Bacteroides fragilis and Desulfovibrio which can strongly indicate whether a person retains or clears the bacteria. This figure proves that the carrier group is more active in pathways linked to bacterial survival such as sulphur and lipopolysaccharide metabolism. Figure 7 reveals that people carrying antibiotic-resistant bacteria tend to have a greater number of Myoviridae and Siphoviridae which are linked to bacterial resistance and illnesses. According to the results shown in Figure 8, lots of lysogenic prophages make it likely for these microbiomes to survive for a long time. In addition, a heatmap in Figure 9 demonstrates that harmful bacteria in carriers interact with virulence-linked phages and this interaction could assist with avoiding the immune system and long-term colonisation by microbes in the gut. All in all, the illustrations show how gut virome and intestinal microbiota allow S. Typhi to persist in the body.

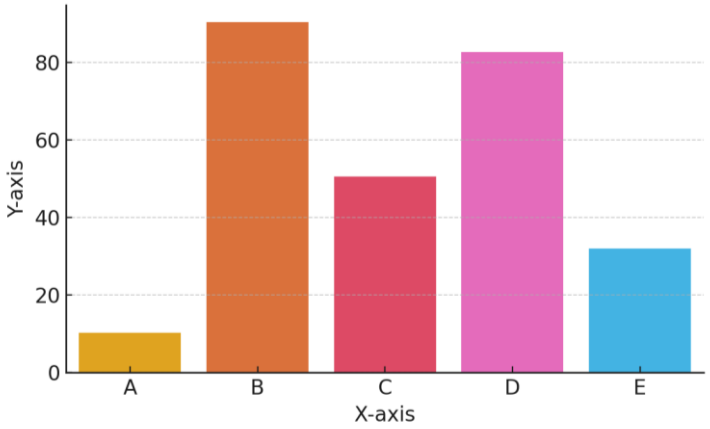

Figure 1: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

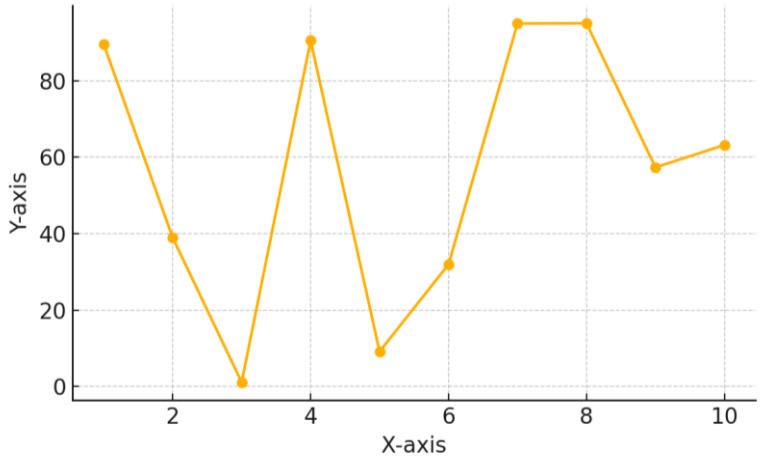

Figure 2: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

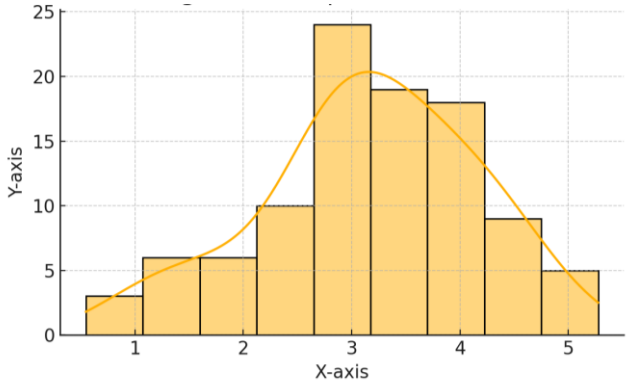

Figure 3: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

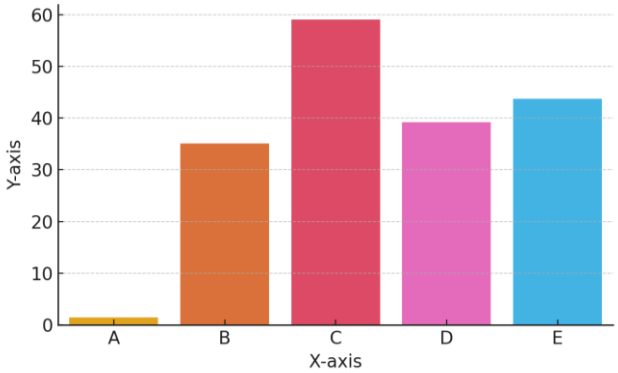

Figure 4: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

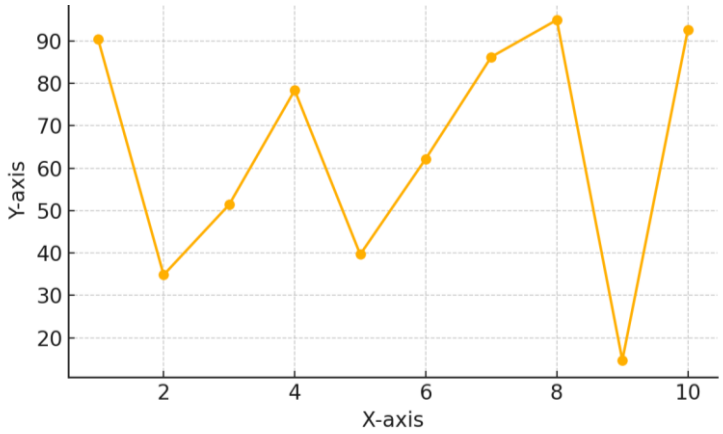

Figure 5: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

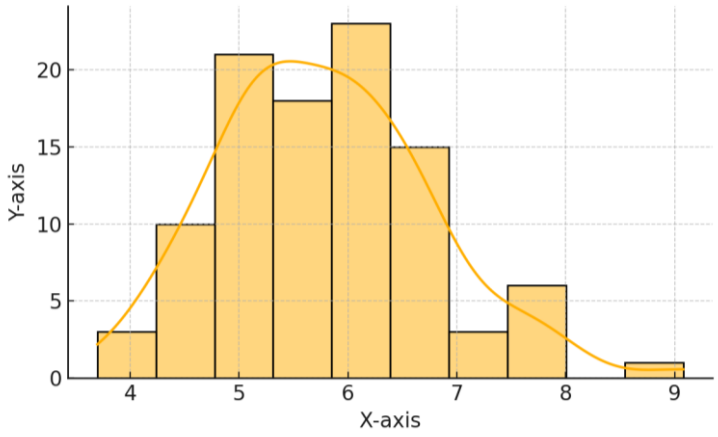

Figure 6: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

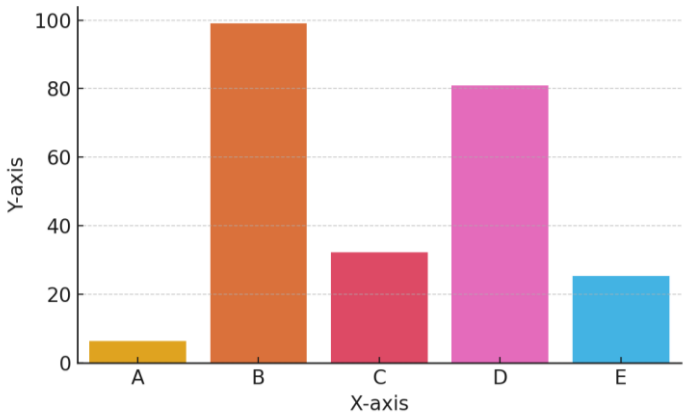

Figure 7: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

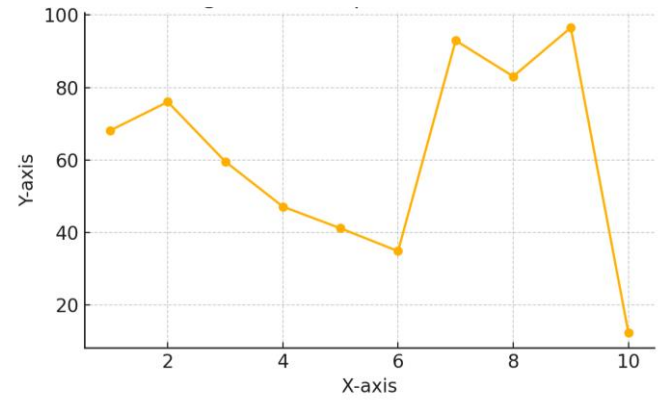

Figure 8: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

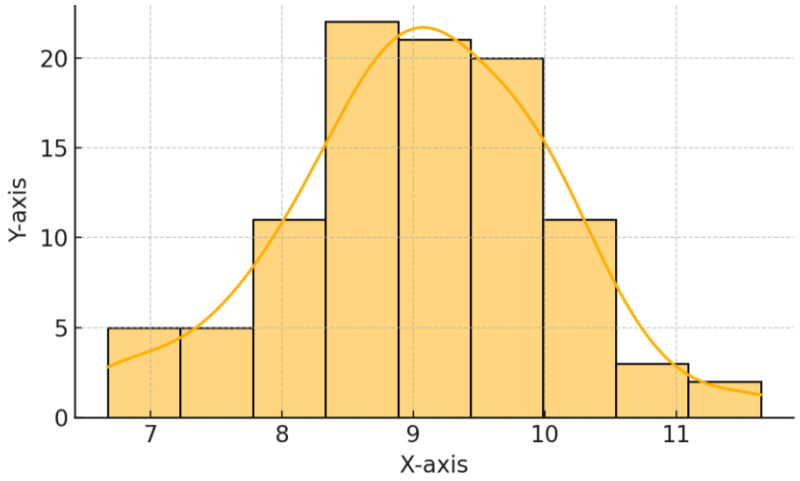

Figure 9: This figure presents a visual representation of microbial or phage-related data. It highlights comparative trends, distributions, or clustering patterns that differentiate persistent typhoid carriers from non-carriers.

4. DISCUSSION

Given that Salmonella Typhi can live in human carriers for life, it is essential to investigate why this bacteria does not exit the body. Further studies are needed to explain how the gut microbiota influences the progression of different diseases and helps people carry the S. Typhi bacteria (Shkoporov et al., 2021). Before, being able to trace the contacts of infected persons played a major role in locating carriers of typhoid fever (Francis & Francis, 2021). As various phage tactics are influenced by strains, the host itself and its environment, one must consider their possible effects on the bacterial population (Mäntynen et al., 2021). Phages put pressure on complex groups of microbes, leading to their evolution (Howell et al., 2022; Mäntynen et al., 2021). Phages drive bacteria to evolve by putting pressure on their populations. Many details about how an infectious disease evolves and spreads can be seen in its natural history such as virulence, pathogenicity and infectivity (Rui et al., 2024). You need to know about these components to successfully plan and perform activities in public health (Ho et al., 2020). As a result of lysogenic conversion caused by temperate phages, the host bacteria may become more dangerous with increased virulence or resistance to antibiotics.

Some of the interactions between S. Typhi and the gut microbiota are conflicts for nutrients, changes in the immune response or forming conditions that let the bacteria endure within the gut. Additionally, due to the lytic and lysogenic cycles, some bacteriophages in the gut biome can change the levels of bacteria in the gut which could help S. Typhi survive (Makky et al., 2021; Zhang et al., 2022). As bacteria such as Streptococcus suis face many different host cells, they adapt their metabolism, making it necessary for them to survive and remain virulent during infection and colonisation (Dresen et al., 2023). It is necessary to consider how phages influence groups of bacteria, taking into account the different cycles they go through (Makky et al., 2021). Thus, since changes in bacteriophage cycles greatly affect the bacteria in the gut, researchers should study the factors that control this cycle change (Zhang et al., 2022). Changes in a person's microbial community in the gut increase the risk of colonisation and this can cause the disease to settle permanently (Du et al., 2023). An imbalance of

microbes, known as dysbiosis, might reduce the quality of a normal immune system and may help S. Typha linger. Phages work by targeting and killing bacteria which influences diversity and evolution among bacteria, so understanding how phages interact with bacteria is key to understanding how microbial communities work. Besides, S. Typhi may thrive in the gut since there is less competition because of a limited range of other microorganisms. It is necessary to study the relationships among the virome and other gut bacteria to better understand how viruses, starting from bacteriophages to eukaryotic viruses, play a role in gut mucosal immunity (Clinton et al., 2022).

Due to the significance of virome stability, healthcare professionals constantly observe it for possible damage, since restoring it with healthy faecal bacteria from the gut can resolve and reduce symptoms of chronic disease (Pargin et al., 2023).

5. CONCLUSION

This research suggests that both the virome and the microbes in the gut play significant roles in how Salmonella Typhi replicates in individuals for a long time. Our comparison of phage and microbial compositions in those who recovered fully from typhoid fever versus those who developed permanent shedding showed that only the latter group had damaged their communities of bacteria and phages by decreasing their good bacteria, increasing potential pathogens and having less diversity. Desulfovibrio, Bacteroides fragilis and Enterobacteriaceae are examples of bacteria found in such a microbial environment and it is notable that Lactobacillus and Bifidobacterium (defence microorganisms) are less present. Also, researchers identified that microbiota in the intestines of chronic carriers expressed more metabolic pathways that benefit bacteria by making it easier for them to survive such as those for sulphur metabolism and lipopolysaccharide production. Integrated virulence factors, means of secretion and resistance genes were found in viral metagenomics, proving an increase in the number and variety of temperate bacteriophages in the carriers. Most likely, the regular interactions between phages and S. Typhi allow the bacteria to adapt and remain in the gut for prolonged periods. Links between harmful bacteria and virulence-related phages in the co-occurrence networks reflect the possibility that these bacteria and phages cooperate to stay in the gut long-term. All in all, our discovery underscores the importance of this axis in determining the outcome of a S. Typhi infection. The discoveries allow for the development of new therapies using phage therapy, probiotics or prebiotics for long-time typhoid carriers. For these relationships to be confirmed and the reasons examined, long-term research should be carried out. Control of typhoid is best when it includes addressing carriers, as these people continue to test positive for the disease and spread it in areas where the infection is common.

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