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RESEARCH

Analysing the relationship between nutrition and the microbial composition of the oral biofilm - insights from the analysis of individual variability

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Abstract

Background: The influence of nutrition on the oral microbiota has been discussed in the literature, but usually only changes of the mean values are reported. This paper focuses on the variability of patients' reactions.

Methods: Two types of inter-individual variability in such studies and statistical models to estimate them are introduced. Through smart presentation of the estimates from the studies, a better understanding of the data can be obtained. Random effects meta-analyses are used to analyse the heterogeneity in variability across different bacteria.

Results: For the nutrition individually chosen by the participants, we observed an inter-individual variability of the bacterial concentration of three log steps. Given that we found no evidence of heterogeneity in variability across different bacteria, the results can be used to offer recommendations for future studies and compute the number of cases needed.

Conclusions: For studies measuring the concentration change of bacteria as a reaction to nutrition change, the use of replications and analysis of the variability is recommended.

Keywords: meta-analyses; variability; heterogeneity; bacterial concentration

Background

The influence of nutrition on the oral microbiota has been discussed in the literature. While some papers investigate the nutrition-induced change of diverse periodontal parameters [1, 2, 3, 4, 5, 6], others discuss the influence of nutrition on the oral microbiota [7, 8, 9, 10, 11, 12]. Interestingly, the authors usually focus on the change of the mean values rather than the inter-individual discrepancies among patients. In this paper, we aim to demonstrate how the interpretation of such data can benefit from explicitly considering inter-individual variability. Since this individual variability is also a major source of the overall variability determining the power and sample size of such studies, we further discuss general rules for sample size calculation in these studies.

We start by presenting a motivating example. Subsequently, we introduce the two types of inter-individual variability that we can investigate in similar studies and statistical models enabling us to estimate them. We present some techniques to

communicate estimates from the models and illustrate their use by analyzing two different bacteria. Finally, we focus on the heterogeneity in variability across the different bacteria, as the final aim is to provide general recommendations on sample sizes in similar studies.

Methods

In this study funded by the German Research Foundation (DFG) with eleven adults (5 male, 6 female) aged between 21 and 56 years, data concerning nutrition and the microbiota in their oral biofilm were collected over 15 months ([13]). The participants ran through five phases, each of which lasted 3 months, following a specific nutritional protocol. In a first lead-in-phase, the nutrition was not changed. Subsequently, the participants changed to a three-month-long diet (phase 2) with an additional daily consumption of 10 g sucrose in the form of small pieces of rock candy (2 g) 5 times between meals. In phase 3 the nutrition was changed to milk protein-containing meals. In addition to their normal food, they ate 150g of yoghurt three times a day and drunk 100ml milk twice a day. Both the yoghurt and the milk were evenly distributed in the oral cavity and left there for an exposure time of three minutes. In phase 4, the nutrition was changed to a high-fiber diet: the participants consumed altogether 500g of vegetable puree, which again was evenly distributed in the oral cavity and left there for an exposure time of three minutes. In the final phase (phase 5), the participants returned to their normal diet like in the lead-in-phase. An *in-situ* splint system was used to sample the dental plaque. During all phases, the dental biofilm was allowed to grow on enamel slabs over the course of seven days.Subsequently, the splint system was removed for analyses of the dental biofilm, cleaned and after seven days it was re-applied for another seven days. This procedure was repeated three times, resulting in three measurement points per phase (figure 1 based on an earlier version in [13]).

The dental plaque samples were analysed using culture techniques as described in detail in [13], resulting in concentration values between 0 and $4.72 * 10^9$ colony-forming units (CFU) per ml. For the analysis the data were log-10-transformed. The values were set to 4 if the concentration values were below the detection limit of 4. We considered the following microorganism groups (further details and abbreviations in the appendix): aerobic bacteria (faecal contaminants were excluded), aerobic bacteria with faecal contaminants, faecal contaminants, anaerobic bacteria, all with faecal contaminants, all (faecal contaminants were excluded), *Streptococcus oralis* 1, *Streptococcus oralis* 2, *Streptococcus oralis* 3, *Streptococcus mutans*, *Gemella Granulicatella Streptococcus* species pluralis (spp.), *Actinomyces* spp., *Rothia* spp., *Lactobacillus vaginalis, Neisseria* spp., *Capnocytophaga* spp., *HACEK, fungi*, black pigmented Bacteroides spp., non-pigmented Bacteroides spp., *Fusobacterium* spp., *Campylobacter* spp., *Selenomonas* spp., Gram-positive aerobic cocci, Gram-positive aerobic rods, Gram-negative aerobic cocci, Gram-negative aerobic rods, Gram-positive anaerobic cocci, Gram-positive anaerobic rods, Gram-negative anaerobic cocci and Gram-negative anaerobic rods. For some of them (*Streptococcus mutans*, *Lactobacillus vaginalis, fungi*, black and not pigmented bacteria, *Selenomonas* spp., Gram-positive anaerobic cocci and rods), the percentage of values below the detection limit was greater than 75%. We decided to exclude these bacteria due to their

limited variation. In the following paragraphs we refer to each of these groups as one bacterial category.

Inter-individual variation and modeling

In this kind of study, two types of variability are of interest for each bacterial taxa: the inter-individual variability or "normal population variation" of the concentration under the individually-chosen diet and the variability of the individual reaction to a nutrition change. The "normal population variation" reflects how much variation we can expect due to inter-individual variations in eating habits, oral microbiota, etc. However, our main interest lies in how uniformly the participants react to a change in diet. The more uniform the reaction, the better we can generalise a change observed in mean values to all patients. A naive way to analyse the "normal" population variation is to consider the empirical variation across individuals in our phase 1, where there was no change in diet. Similarly, we can analyse the empirical variation of the changes in bacterial concentration after the change in diet. However, both empirical variations also reflect measurement errors and random week-to-week variation. Fortunately, in our study there are built-in repetitions within each phase, which enables a direct estimate of the inter-individual variation by appropriate modeling.

In the following, we denote the eleven participants with i, the five phases with p and the three repetitions with r. We consider the following model for the log-10-transformed concentrations Y_{ipr} of a bacterial category

$$Y_{ipr} = \alpha_i + \Delta_{ip} + \epsilon_{ipr} \tag{1}$$

with α_i reflecting the individual initial level of phase 1, Δ_{ip} the incremental changes compared with phase 1 and ϵ_{ipr} representing the measurement error and within-person biological variability. We further assume $\alpha_i \sim N(\mu_\alpha, \sigma_\alpha^2)$, $\Delta_{ip} \sim N(\mu_{\Delta_p}, \sigma_{\Delta_p}^2)$, $\epsilon_{ipr} \sim N(0, \sigma_{res}^2)$ for $p = 2, ..., 5$ and independence of these quantities. The parameters of interest are the initial mean value μ_α, the mean values of the incremental changes μ_{Δ_p} per phase, the standard deviation σ_α, describing the inter-individual variability at the initial level and the standard deviations σ_{Δ_p} characterising the variability in the individual reaction to a change in diet for each phase. Given that the phase-specific standard deviations σ_{Δ_p} are difficult to estimate due to the small sample size, a model based on the assumption that all standard deviations σ_{Δ_p} are equal to a common value σ_Δ also is fitted. For model fitting, we use the REML technique [14].

Guidance to interpretation

Standard deviations are difficult to interpret for non-statisticians. Therefore we make use of three techniques to assist non-statisticians in their interpretation. First, if a random variable z is drawn from a normal distribution with mean μ and a standard deviation σ, the interval $\mu \pm 1.96\sigma$ covers 95% of all observations of z. We refer to this as the 95% range of z. We can apply this to both the initial values ($z = \alpha_i, \mu = \mu_\alpha, \sigma = \sigma_\alpha$) as well as the increments ($z = \Delta_i, \mu = \mu_{\Delta_p}, \sigma = \sigma_\Delta$). A similar measure is used in [15] and is called 95% random effects confidence interval.

Second, we consider the probability that a single observation of z is above a constant c, which is given by

$$P(z > c) = 1 - \Phi(\frac{c - \mu}{\sigma}). \tag{2}$$

We apply this to the incremental changes with $c = 0$, as in this instance we are interested in knowing the probability of a positive (or negative) reaction to a change. More precisely we are interested in a measure that reflects the coherence of individual changes with the mean change. Accordingly, if $\mu > 0$ we are interested in $P(z > 0)$, if $\mu < 0$ in $P(z < 0)$.

Consequently, we define the coherence η_p of the individual changes with the mean change for each phase p as:

$$\eta_p = \begin{cases} 1 - \Phi(\frac{-\mu_{\Delta_p}}{\sigma_{\Delta_p}}) & \text{if } \mu_{\Delta_p} > 0 \\ \Phi(\frac{-\mu_{\Delta_p}}{\sigma_{\Delta_p}}) & \text{otherwise.} \end{cases} \tag{3}$$

Third, we consider the expected absolute difference for two randomly-chosen values z_1 and z_2, which is equal to 1.13 times the standard deviation (a derivation is given in the appendix). We denote this in the following with E_{diff}. For example, if we apply this to the true initial values α_i, E_{diff} is equal to the difference that can be expected if we consider two randomly chosen individuals.

Heterogeneity in individual variation

To use results on inter-individual variability with respect to the planning of studies, it is desirable to derive conclusions that are valid independent of the choice of the bacterial category. Hence, it is of interest to investigate the heterogeneity of variations across the bacteria. We approach this by random effects meta-analyses of the estimated standard deviations considering each bacterial category as a "study".

Such a meta-analysis is based on the model

$$log\ \widehat{SD}_b = log\ SD_b + \epsilon_b \text{ with } \epsilon_b \sim N(0, \sigma_b^2) \text{ and } log\ SD_b \sim N(\mu, \tau^2) \tag{4}$$

where $log\ SD_b$ is the logarithm of the true standard deviation of a bacterial category b, σ_b the true standard error of $log\ \widehat{SD}_b$, which we replace by its estimate, μ the average $log\ SD$ and τ the standard deviation of the true $log\ SD$ values. τ allows us to judge the heterogeneity of the true standard deviations between the bacteria. In particular, with the technique explained above we can build a 95% range for the true standard deviations based on τ that illustrates the variation. In addition, we will try to identify sources for the variation, including by examining the relation to the initial mean value.

Sample size

We will use the results of our study to perform a sample size calculation for further studies. If we are interested in a sample size calculation for a study examining the results of two different diets on the bacterial concentration of a single strain of

bacteria in a paired design, we can link this scenario to our study comparing phase p with the initial phase. The mean value $\mu = E[D_i]$ and the variance $\sigma^2 = Var(D_i)$ of the individual differences $D_i = \bar{Y}_{ip} - \bar{Y}_{i1}$ have to be specified for a sample size calculation.

In the case of R repetitions per phase and participant, we have

$$\begin{aligned} &\sigma^2 = Var(\bar{Y}_{ip} - \bar{Y}_{i1}) \\ &= Var\tfrac{1}{R}\textstyle\sum_{r=1}^{R}(\alpha_{i_1} + \Delta_{ip} + \epsilon_{ipr} - \alpha_{i_1} - \epsilon_{i1r}) \\ &= \tfrac{1}{R^2}Var(R\Delta_{ip} + \textstyle\sum_{r=1}^{R}\epsilon_{ipr} - \epsilon_{i1r}) \\ &= \tfrac{1}{R^2}(R^2\sigma^2_{\Delta_p} + 2R\sigma^2_{res}) \\ &= \sigma^2_{\Delta_p} + \tfrac{2}{R}\sigma^2_{res}. \end{aligned} \tag{5}$$

The choice of μ will be discussed later. The sample size for a power of 0.9 and a significance level of $\alpha = 0.05$ will be computed using the formula of Chow, S.-C., J. Shao, and H. Wang [16].

Software

For the analyses, the statistics program STATA 15.1 (StataCorp LT, College Station, TX, USA) is used. For estimates of means and standard deviations, the *xtmixed* procedure with the option *reml* is applied after rewriting model (1) in terms of fixed and random effects. Meta-analyses are performed by the method of DerSimonian & Laird [17] using a random effects model, provided in STATA as the *metan* command with the options *random* and $eform$ for log transformed values. For graphical presentation, scatter plots and forest plots are used.

Results

Illustrative applications

First, we illustrate the application of our approach based on the example of two specific bacterial categories: anaerobic bacteria and *Rothia* spp. (results in Table 1). The results for all bacteria can be found in Tables 2 and 3. For a first overview of the individual distribution of the yielded data, scatter plots of the bacterial concentrations against the time for each individual were developed. Figures 2 and 3 show anaerobic bacteria and *Rothia* spp., respectively (the other bacterial groups can be found in additional file 1 of the supplementary material). For anaerobic bacteria, we obtain an initial mean value $\hat{\mu}_\alpha$ of 6.64 and a $\hat{\sigma}_\alpha$ of 1 describing the inter-individual variability of the initial level. This means the individual initial values have a 95% range of $[4.68, 8.60]$. Since we used logarithmic values, this implies that the participants at opposing ends of the distribution have a difference of up to four log steps. The $\hat{\mu}_\alpha$ as well as the $\hat{\sigma}_\alpha$ of *Rothia* spp. is lower with values at 5.83 and 0.44 respectively; hence, the initial values are much more homogenous, which can also be seen in the smaller 95% range of $[4.97, 6.69]$. Next, we consider how uniformly the participants react to a change in diet. For anaerobic bacteria the largest mean change can be observed from phase 1 to phase 5 with -0.741, while for *Rothia* spp. the largest change occurs between phase 1 and phase 2 with a value of 0.639. The variability in the individual reaction to a change was first estimated for each of the phases ($\hat{\sigma}_{\Delta_2}, \hat{\sigma}_{\Delta_3}, \hat{\sigma}_{\Delta_4}, \hat{\sigma}_{\Delta_5}$). These estimates are quite unstable,

as can be seen in the wide confidence intervals. Therefore, we prefer to consider the common standard deviation for all increments $\hat{\sigma}_\Delta$, which we can estimate with higher precision and thus smaller confidence intervals. For anaerobic bacteria, we observe a $\hat{\sigma}_\Delta$ of 0.54 and for *Rothia* spp. a smaller value of 0.29, which suggests that the effects for *Rothia* spp. are more homogenous. We can combine this with the mean values observed at different phases. For anaerobic bacteria, we obtain a 95% range for the individual increments from phase 1 to phase 5 of [-1.80, 0.32] with 0 inside the range, while for *Rothia* spp. the 95% range for the individual increments from phase 1 to phase 2 is narrower with [0.07, 1.21].

If we look at the coherence η_p of the individual increments with the mean effect for each phase as introduced above, for anaerobic bacteria we observe only one value above 90%, while for *Rothia* spp. for all phases with the exception of phase 4 high values are reached. This can also be seen in the scatterplots (figure 2 and 3): for *Rothia* spp. all participants show the same reaction to a change in diet in each phase in the form of a decrease or increase, while for anaerobic bacteria different reactions are observed.

Heterogeneity

Heterogeneity in the standard deviation of the initial values

A meta-analysis of the estimated standard deviation $\hat{\sigma}_\alpha$ of the initial values (figure 4) was performed. Each bacterial category here corresponds to a study. Four studies in which the standard error was not estimable were excluded. The most important outcome of this meta-analysis is that we obtain an estimated τ of 0, which means that there is no evidence of heterogeneity across the different bacterial groups. As the result of the meta-analysis, we obtain an overall value for σ_α of 0.79, which means that the initial values have a typical range of three log steps (mean initial value $\pm 0.79 * 1.96$).

Heterogeneity in the standard deviation of the increments

Looking at the meta-analysis of the standard deviations of the increments (figure 5), we observe again a τ of 0. Larger confidence intervals can be found for the bacteria 3, 10 and 12. The overall value of σ_Δ is 0.5, which we will use for sample size calculations.

Heterogeneity in the standard deviation of the residuals

In the meta-analysis of the standard deviations of the residuals (figure 6), we obtain a τ of 0.26. With the exception of numbers 1, 2, 5, 6, 7 and 18, we observe rather homogenous values. Looking at figure 7, we observe smaller residuals for bacterial groups with a large initial mean value. These bacterial groups correspond to the aforementioned bacterial groups. This is not particularly surprising because they do not represent single bacteria but rather relatively large bacterial groups. Hence, the residuals are smaller due to averaging over many bacteria. We obtain an overall σ_{res} of 0.87 with a 95% range of [0.52, 1.45] for σ_{res}. If we exclude the bacterial groups with large initial mean values, we observe a smaller τ of 0.11 and an overall σ_{res} of 1.0 with a 95% range of [0.79, 1.21] for σ_{res}. For the bacteria groups with large initial mean values, we obtain a τ of 0.14 and an overall σ_{res} of 0.59 (95%

range [0.32, 0.86]). To illustrate the influence of σ_{res} on the sample size calculation, both values 0.6 (for larger bacterial groups) and 1.0 (for single bacteria) are used.

Sample size considerations

As pointed out in the methods part, for a study comparing two diets in a paired design the variance of the final estimates depends on the population standard deviation σ_Δ, the standard deviation of the residuals σ_{res} and the number of repetitions R. Equation (5) indicates that the variance decreases with increasing R, but in any case there remains the contribution of the population standard deviation. For a sample size consideration we have to specify values for the standard deviations σ_Δ and σ_{res} for the mean differences μ and the repititions R. Our considerations about the heterogeneity of the different standard deviations across the bacterial groups suggest using a σ_Δ of 0.5 and a σ_{res} of 0.6 and 1, respectively. With respect to the choice of μ, we should take into account the clinical context. However, little is known about the impact of changes in the microbiota on the individual. From a statistical perspective, we argue that a relevant effect should explain some of the overall variation between individuals. A useful benchmark may be the expected difference in initial values between two randomly-chosen individuals. This is a simple function of the population standard deviation σ_α, (namely 1.13*σ_α, as pointed out in the Appendix). We have seen that there is no substantial variation in σ_α, and hence we can use the estimated value $\hat{\sigma}_\alpha = 0.79$, resulting in $\mu = 0.89 \approx 0.9$. However, this value is rather large compared with effects observed in other studies [4, 18] and what we observed as effect estimates in our study. In former studies, Tenuta et al.[18] found a change of biofilm in glucose + fructose and sucrose groups in comparison with a negative control group and Filoche et al. [4] found that plaque from different donors showed a different reaction to sucrose. The results of Tenuta for the mean concentration of *S. mutans* (log 10-transformed to be comparable with our results: negative control: 2.04; treatment with glucose + fructose: 2.81; treatment with sucrose: 2.63) indicate that changes in the range of a half log-10 step seem realistic. Therefore, we also consider the values 0.7 and 0.5. In Table 4, we report the sample size for different combinations of μ, σ_Δ, σ_{res} and a varying number of repetitions R. The use of repetitions allows for a substantial decrease in the number of study participants: the use of two repetitions already leads to a reduction of approximately 40% and a slight increase in the number of measurements. If we look back at the variance formula in the methods part, we see that $\sigma_{res} \approx 2 * \sigma_\Delta$ (thus $\sigma^2_{res} \approx 4 * \sigma^2_\Delta$), resulting in σ_Δ having only a minor influence on the sample size. If costs per measurement are lower than the costs per study participant, even more repetitions can save costs. The overall sample size depends on the choice of μ. Our study ($R = 3, \sigma_\Delta = 0.5, \sigma_{res} = 1$) was powered to detect a difference in the magnitude of 0.9. In order to also detect moderate differences, one should conduct more than 90 measurements.

Discussion

Our results show that an analysis of participants' variation regarding bacterial concentration as a result of a change in diet is feasible and useful. The estimation of

inter-individual variation is possible if some repetitions of the observations are made and allows for more information in analysing single bacteria.

In most studies, the authors usually look at the change of the mean values and interpret it as general differences. Standard deviations of the incremental changes offer full insights. In particular, the coherence of the individual increments with the mean change allows for a better understanding of one's own results. If we look at the η_p for the single phases in Table 3, in two cases we even obtain values of $\eta_p < 86\%$ for significant effects. On the other side there are also non-significant mean changes with a high coherence. In Table 5, we computed η for realistic values of μ and σ. Tables like this can help to classify one's own results. We can see that with a small μ and a relatively large σ, no uniform reaction of the participants can be expected.

For the initial values, we typically observe an inter-individual variability of three log-10 steps. This is not particularly surprising because Aas et al. [19] have already observed differences of the bacterial flora in the healthy oral cavity, even between different oral sites of the same person.

The standard deviations of the increments were smaller than those of the residuals, although all of the analyzed values show a comparable reaction for different bacteria. Putting aside the fact that repetitions can reduce the costs of a study, they are absolutely necessary to estimate all of the measures above.

Due to the homogenously-estimated standard deviations, of both the increments, the residuals and the initial values for different bacteria, the results can be used for planning new studies. If the concentration of bacteria as a reaction to a change in diet similar to the setup in our study should be examined, and a mean difference of half a log-10 step should be shown, we recommend recruiting 31 participants and three repetitions per phase. For the analyses of the data, the proposed 95% ranges and coherence measures η should be computed to make the results more clear. For some bacterial groups, we observed lower standard deviations of the residuals than for others due to the fact that we sometimes grouped bacteria together into sub-categories. This point should be incorporated into the planning of a study because smaller sample sizes are required for bacterial groups than for single bacteria.

Due to the small sample size, our motivating study has some limitations. We have already argued above that the standard deviations of the increments for the single phases are quite unstable. Another limitation is that often values were below the detection limit. Due to the small sample size, the use of multilevel mixed-effects tobit regression for continuous responses, where the outcome variable is censored with the detection limit as a censoring limit was not possible. In this paper we focused on the analysis of single bacteria groups. However, also understanding the change of the whole bacteria spectrum is of interest. This requires to extend the ideas presented in this paper to a multivariate setting. Our proposal already supplements the recommendation for heterogeneity measures for logistic regression models by Larsen et al. [20]. However, further research is needed.

Conclusions

For studies measuring the concentration change of bacteria as a reaction to nutrition change, the use of replications and analysis of the variability is recommended. Our suggestions contribute to a better understanding of the individual variation in bacterial concentrations and to a more targeted planning of new studies.

Abbreviations
The following abbreviations were used in the manuscript: spp. = species pluralis, Str = *Streptococcus* spp., Gem = *Gemella* spp. , Act = *Actinomyces* spp. , Lact vagin = *Lactobacillus vaginalis* , Neiss = *Neisseria* spp. , Capn = *Capnocytophaga* spp. , Haem = *Haemophilus* spp. , Cardiobact = *Cardiobacter* spp. , Citrob = *Citrobacter* spp. , Esch = *Escherichia* spp. , Entero = *Enterobacter* spp. , Kleb = *Klebsiella* spp. , Prev = *Prevotella* spp. , Fuso = *Fusobacterium* spp. , C = *Campylobacter* spp. , Veillo = *Veillonella* spp. , Atop = *Atopobium* spp. , Ols = *Olsenella* spp. , Prop = *Propionibacterium* spp. , Parvi = *Parvimonas* spp. , Bact = *Bacteroides* spp. , Parvi micra = *Parvimonas micra*, aerob fce = aerobic bacteria without faecal contaminants, aerob wfc = aerobic bacteria with faecal contaminants, all wfc = all bacteria with faecal contaminants, all fce = all bacteria without faecal contaminants , Gn = Gram-negative, Gp = Gram-positive

Declarations
Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the University of Freiburg (Nr. 237/14). A written informed consent was obtained from all participants. All experiments and data collections were performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable

Availability of data and material
The data have not been completely analyzed until now. Further publications are in preparation.

Competing interests
The authors declare that they have no competing interests.

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Author's contributions
A.A.A., A.A., J.P.W. and E.H. designed the original study. L.K., A.A. and A.W. coordinated the sample collection, L.K. and A.A. participated in data analysis and drawed the manuscript. A.A designed figure 1. K.V. had the idea for the topic, performed the statistical analysis and designed the remaining figures. All authors edited the manuscript and approved the final article.

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Figures

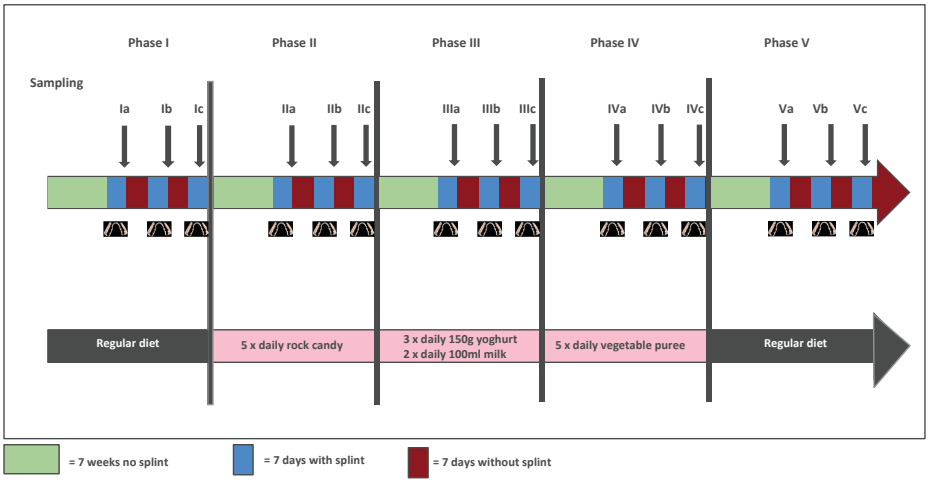

Figure 1 Study design: Description of the sampling and nutrition during the five phases.

Tables

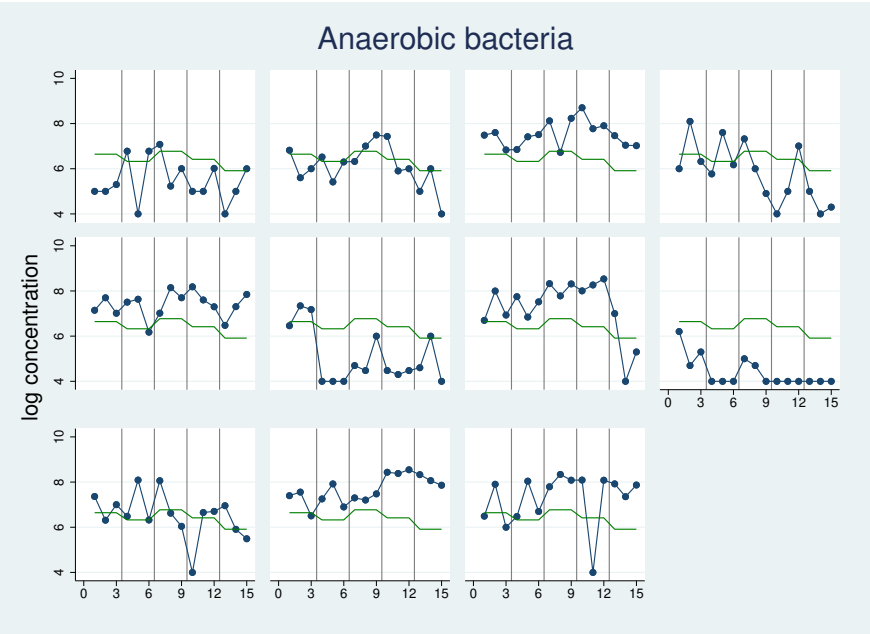

Figure 2 Example scatter plot of individual bacterial concentrations over time. Concentrations (in log-10 CFU per ml) of anaerobic bacteria for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

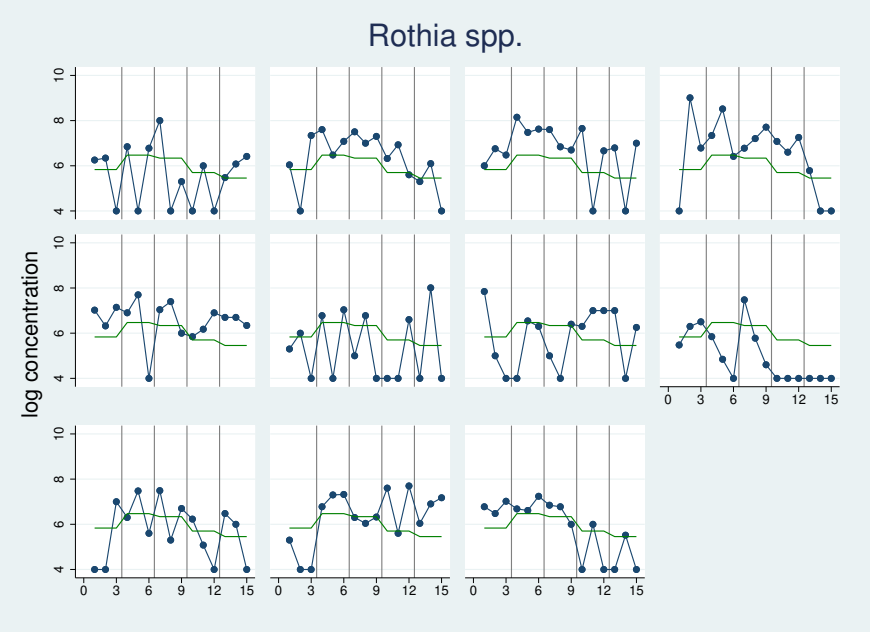

Figure 3 Example scatter plot of individual bacterial concentrations over time. Concentrations (in log-10 CFU per ml) of *Rothia* spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

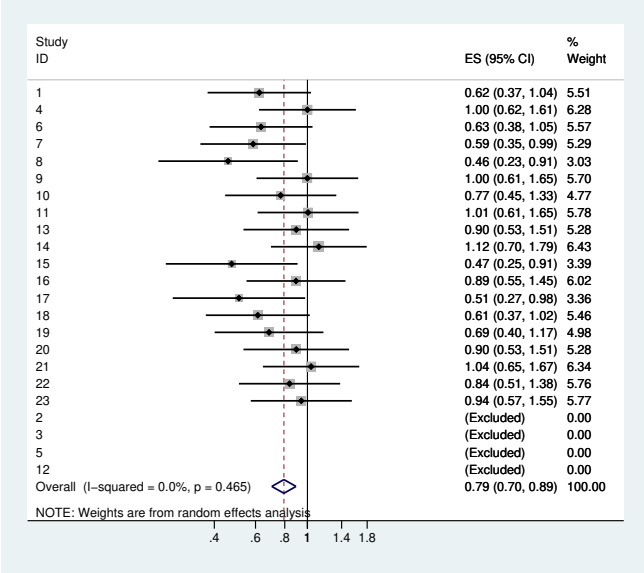

Figure 4 Meta-analysis of the standard deviations of the initial values. Each study represents one bacterial category.

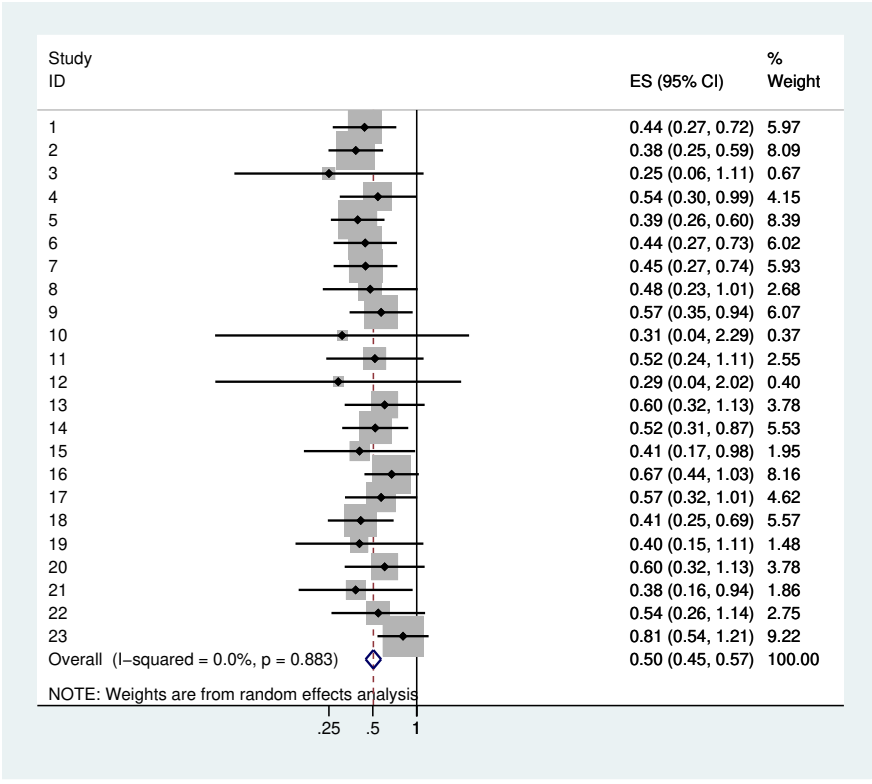

Figure 5 Meta-analysis of the standard deviations of the increments. Each study represents one bacterial category.

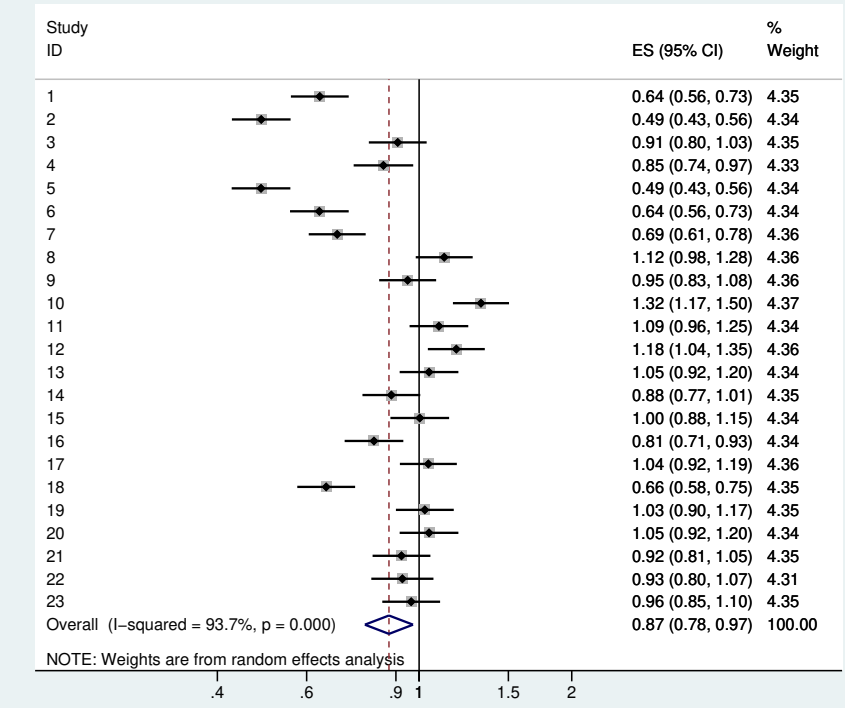

Figure 6 Meta-analysis of the standard deviations of the residuals. Each study represents one bacterial category.

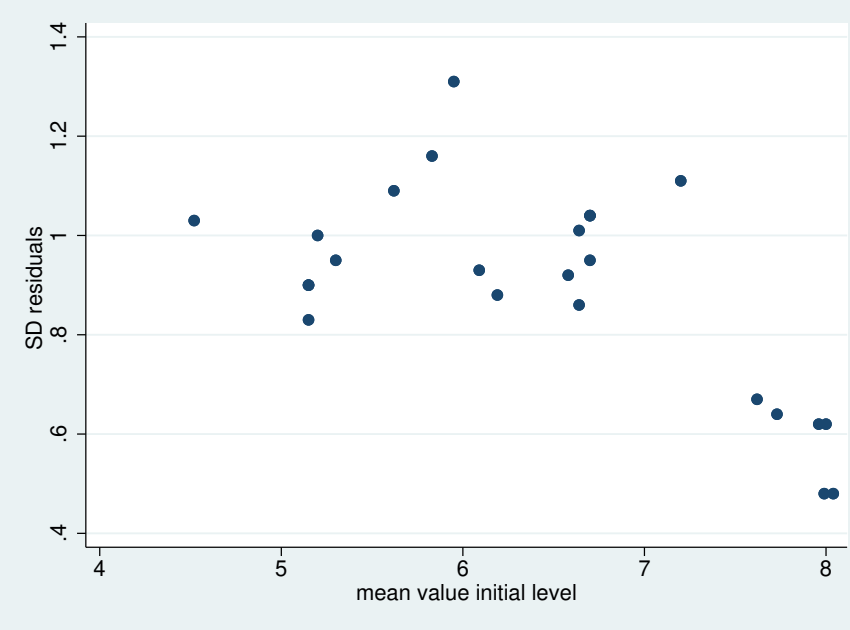

Figure 7 Mean value of initial value and standard deviation of the residuals.

Estimate	Anaerobic bacteria		Rothia spp.	
	Estimate	95% CI	Estimate	95% CI
Initial Values				
$\hat{\mu}_\alpha$	6.644	[5.995, 7.294]	5.833	[5.355, 6.312]
$\hat{\sigma}_\alpha$	1.000	[0.621, 1.611]	0.435	[0.212, 0.888]
Increments				
$\hat{\mu}_{\Delta_2}$	-0.319	[-0.840, 0.201]	0.639	[0.042, 1.235]
$\hat{\mu}_{\Delta_3}$	0.129	[-0.392, 0.649]	0.506	[-0.091, 1.102]
$\hat{\mu}_{\Delta_4}$	-0.269	[-0.790, 0.251]	-0.132	[-0.729, 0.464]
$\hat{\mu}_{\Delta_5}$	-0.741	[-1.262, -0.221]	-0.377	[-0.973 , 0.219]
$\hat{\sigma}_{\Delta_2}$	0.209	[0.004, 10.142]	0.000	[0, ∞]
$\hat{\sigma}_{\Delta_3}$	0.000	[0.000, 0.404]	0.000	[0, ∞]
$\hat{\sigma}_{\Delta_4}$	0.681	[0.321, 1.448]	0.605	[0, ∞]
$\hat{\sigma}_{\Delta_5}$	0.720	[0.354, 1.463]	0.556	[0, ∞]
$\hat{\sigma}_\Delta$	0.542	[0.297, 0.990]	0.290	[0.041, 2.018]
Other measures				
η_2	72.3		98.6	
η_3	59.5		96.1	
η_4	69.1		67.3	
η_5	91.5		90.5	

Table 1 Model-based estimates: Mean values and standard deviations of the initial values and increments for anaerobic bacteria and *Rothia* spp. with 95% CI. $\hat{\sigma}_\Delta$ indicates the common SD for the increments of phase 2-5. η_i coherence of the individual values with the mean effect per phase.

Bacteria		initial values		increments								
Nr	Name	$\hat{\mu}_\alpha$	$\hat{\sigma}_\alpha$	$\hat{\sigma}_\Delta$	$\hat{\sigma}_{\Delta_2}$	$\hat{\sigma}_{\Delta_3}$	$\hat{\sigma}_{\Delta_4}$	$\hat{\sigma}_{\Delta_5}$	$\hat{\mu}_{\Delta_2}$	$\hat{\mu}_{\Delta_3}$	$\hat{\mu}_{\Delta_4}$	$\hat{\mu}_{\Delta_5}$
1	Aerob fce	7.96	.62	.44	.35	0	.43	.81	-.06	.11	-.21	-.72
2	Aerob wfc	7.99	.52	.38	0	0	.38	.68	.08	.11	-.13	-.58
3	Faecal contaminants	5.15	.45	.25	.58	0	.28	0	.2	.5	.54	.48
4	Anaerobic bacteria	6.64	1	.54	.21	0	.68	.72	-.32	.13	-.27	-.74
5	All wfc	8.04	.53	.39	0	0	.41	.70	.06	.13	-.11	-.57
6	All fce	8	.63	.44	.33	0	.45	.82	-.08	.13	-.18	-.71
7	Str oralis 1	7.62	.59	.45	.33	0	.56	.79	.03	.21	-.19	-.65
8	Str oralis 2	7.2	.46	.48	0	.55	.3	.8	-.12	.05	-.01	-.53
9	Str oralis 3	6.7	1	.57	.28	.32	.65	.87	.1	.33	-.39	-.97
10	Gem Granulicatella Str	5.95	.77	.31	0	.62	.33	.45	-.23	.22	-.12	-.19
11	Act	5.62	1.01	.52	0	.56	.62	.67	.43	.67	.48	-.70
12	Rothia spp.	5.83	.44	.29	0	0	.6	.56	.64	.51	-.13	-.38
13	Neiss spp.	6.7	.9	.6	.48	.56	.82	.56	-.34	-.99	-.8	-1.16
14	Capn spp.	6.19	1.12	.52	.48	.37	.47	.67	-.38	-.55	-.83	-1.14
15	HACEK	5.2	.47	.41	.59	0	.45	.42	.3	-.84	-.61	-.57
16	Fuso spp.	5.15	.89	.67	0	.8	.32	.81	-.08	-.30	.02	-.47
17	C spp	4.52	.51	.57	0	.8	.83	.23	.17	.06	.54	.08
18	Gp aer cocci	7.73	.61	.41	.26	0	.4	.77	-.01	.17	-.15	-.64
19	Gp aer rods	6.64	.69	.41	0	0	.64	.71	.24	.35	-.14	-.81
20	Gn aer cocci	6.7	.9	.6	.48	.56	.82	.56	-.34	-.99	-.8	-1.16
21	Gn aer rods	6.58	1.04	.38	0	.3	.32	.67	-.29	-.86	-1.05	-1.35
22	Gn anaer cocci	6.09	.84	.55	.35	0	.81	.55	-.02	.46	.06	-.32
23	Gn anaer rods	5.3	.94	.81	0	1.15	.67	.8	.24	-.21	.22	-.41

Table 2 Model-based estimates: Mean values and standard deviations of the initial values and increments. $\hat{\sigma}_\Delta$ indicates the common SD for the increments of phase 2-5. All abbreviations can be found in the list of abbreviations at the end of the manuscript.

bacteria	η_2	η_3	η_4	η_5	σ_{res}
Aerob fce	.	59.9	68.3	94.9 *	.62
Aerob wfc	.	61.4	63.4	93.7 *	.49
Faecal contaminants	78.8	97.7 *	98.5 *	97.3 *	.91
Anaerobic bacteria	72.3	59.5	69.1	91.5 *	.85
All wfc	.	63.1	61.1	92.8 *	.49
All fce	.	61.6	65.9	94.7 *	.64
Str oralis 1	.	68.0	66.4	92.6 *	.69
Str oralis 2	59.9	.	.	86.5	1.12
Str oralis 3	57.0	71.9	75.3	95.6 *	.95
Gem Granulicatella Str	77.1	76.1	65.1	73.0	1.32
Act	79.6	90.1 *	82.2	91.1 *	1.09
Rothia spp.	98.6 *	96.1	67.3	90.5	1.18
Neiss spp.	71.5	95.1 *	90.9 *	97.3 *	1.05
Capn spp.	76.8	85.8 *	94.5 *	98.6 *	.88
HACEK	76.8	98.0 *	93.2 *	91.8 *	1.0
Fuso spp.	.	67.3	.	75.9	.81
C spp	61.7	.	82.8	.	1.04
Gp aer cocci	.	66.1	64.3	94.1 *	.66
Gp aer rods	72.1	80.3	63.4	97.6 *	1.03
Gn aer cocci	71.5	95.1 *	90.9 *	97.3 *	1.05
Gn aer rods	77.7	98.8 *	99.7 *	100 *	.92
Gn anaer cocci	.	79.9 *	.	72.0	.93
Gn anaer rods	61.6	60.2	60.7	69.4	.96

Table 3 η_i coherence of the individual values with the mean effect per phase; η was not computed if $|\mu_{\Delta_p}| < 0.1$; σ_{res} residuals. $*$ indicates significant effect. All abbreviations can be found in the list of abbreviations at the end of the manuscript.

μ	R	sample size / number observations	
		$\sigma_{res} = 0.6$	$\sigma_{res} = 1$
0.9	1	12/12	24/24
	2	9/18	15/30
	3	7/21	11/33
	4	7/28	10/40
0.7	1	18/18	39/39
	2	12/24	23/46
	3	10/30	17/51
	4	9/36	15/60
0.5	1	33/33	73/73
	2	22/44	42/84
	3	18/54	31/93
	4	16/64	26/104

Table 4 Sample size and number of observations for $\sigma_\Delta = 0.5$ and different μ, σ_{res} and R.

	σ		
μ	0.3	0.5.	0.7
0.3	84.1	72.6	66.6
0.5	95.2	84.1	76.2
0.7	99.0	91.9	84.1
0.9	99.9	96.4	90.1

Table 5 η for some μ and σ-combinations.

Appendix

Description of the bacteria classes:

- Aerob fce: Str *oralis*, Str *mitis*, Str *infantis*, Str *sanguinis*, Str *parasanguinis*, Str *australis*, Str *peroris*, Str *gordonii*, Str *salivarius*, Str *vestibularis*, Str *anginosus* group, Str *mutans*, Gem *morbillorum*, Gem *haemolysans*, Gem *sanguinis*, *Granulicatella adiacens, Granulicatella elegans, Abiotrophia defectiva*, Act *oris*, Act *odontolyticus*, Act *dentalis*, Act *georgiae*, Act *naeslundii*, Act spp, *Rothia mucilaginosa, Rothia dentocariosa, Rothia aeria, Corynebacterium* spp., Lact *vagin*, Neiss *macacae/mucosa*, Neiss *oralis*, Neiss *subflava*, Neiss *bacilliformis*, Neiss *elongata*, Neiss *flavescens*, Neiss spp, Neiss *perflava*, Neiss *cinerea, Lautrop mirabilis*, Capno *granulosa*, Capno *gingivalis*, Capno *ochracea*, Capno *sputigena*, Capno spp., Haem *haemolyticus*, Haem *parahaemolyticus*, Haem *parainfluenzae*, Haem *influenzae*, Cardiobact *hominis, Eikenella corrodens, Kingella spp, Candida albicans*
- Aerob wfc: Str *oralis*, Str *mitis*, Str *infantis*, Str *sanguinis*, Str *parasanguinis*, Str *australis*, Str *peroris*, Str *gordonii*, Str *salivarius*, Str *vestibularis*, Str *anginosus* group, Strep *mutans*, Gem *morbillorum*, Gem *haemolysans*, Gem *sanguinis*, *Granulicatella adiacens, Granulicatella elegans, Abiotrophia defectiva*, Act *oris*, Act *odontolyticus*, Act *dentalis*, Act *georgiae*, Act *naeslundii*, Act sp, *Rothia mucilaginosa, Rothia dentocariosa, Rothia aeria, Corynebacterium* spp, Lacto *vagin*, Neiss *macacae/mucosa*, Neiss *oralis*, Neiss *subflava*, Neiss *bacilliformis*, Neiss *elongata*, Neiss *flavescens*, Neiss spp, Neiss *perflava*, Neiss *cinerea*, *Lautrop mirabilis*, Capno *granulosa*, Capno *gingivalis*, Capno *ochracea*, Capno *sputigena*, Capno spp, HaemHaem *haemolyticus*, Haem *parahaemolyticus*, Haem *parainfluenzae*, Haem *influenzae*, Cardiobact *hominis, Eikenella corrodens, Kingella* spp, *Candida albicans*, Citrob *freundii*, Citrob *koseri* , Esch *coli*, Entero *asburiae*, Entero *cloacae* complex, Kleb *oxytoca*, Kleb *variicola*, Kleb *pneumoniae, Serratia marcescens*
- Faecal contaminants: Citrob *freundii*, Citrob *koseri*, Esch *coli*, Entero *asburiae*, Entero *cloacae* complex, Kleb *oxytoca*, Kleb *variicola*, Kleb *pneumoniae, Serratia marcescens*
- Anaerobic bacteria: *Porphyromonas* spp., Prev *intermedia*, Prev *nigrescens*, Prev *histicola*, Prev *melaninogenica*, Prev *loescheii*, *Prevotella* spp., nipig Bact spp., Prev *salivae*, Fuso *nucleatum*, Fuso *periodontium* , C *rectus*, C *concisus*, C *showae*, C spp, *Selenomonas* spp, Veillo *parvula*, Veillo *dispar*, Veillo *rogosa*, Veillo *atypica*, *Megasphaera micronuciformis*, Atop *rimae*, Atop *parvulum, Filifactor alocis, Solobacterium moorei, Lachnoanaerobaculum orale, Lachnoanaerobaculum saburreum*, Ols *profusa*, *Catonella morbi clone*, Prop *acnes, Eubacteium yurii*, Parvi *micra*
- All wfc: aerob wfc + *Porphyromonas* spp., Prev *intermedia*, Prev *nigrescens*, Prev *histicola*, Prev *melaninogenica*, Prev *loescheii*, *Prevotella* spp, nipig Bact spp., Prev *salivae*, Fuso *nucleatum*, Fuso *periodontium*, C *rectus*, C *concisus*, C *showae*, C spp, *Selenomonas* spp, Veillo *parvula*, Veillo *dispar*, Veillo *rogosa*, Veillo *atypica, Megasphaera micronuciformis*, Atop *rimae*, Atop *parvulum, Filifactor alocis, Solobacterium moorei, Lachnoanaerobaculum orale, Lachnoanaerobaculum saburreum, Ols profusa Catonella morbi clone*, Prop *acnes, Eubacteium yurii*, Parvi micra
- All fce: aerob wfc + *Porphyromonas* spp., Prev *intermedia*, Prev *nigrescens*, Prev *histicola*, Prev *melaninogenica*, Prev *loescheii, Prevotella* spp., nipig Bact spp., Prev *salivae, Fuso nucleatum, Fuso periodontium*, C *rectus*, C *concisus*, C *showae*, C spp., *Selenomonas* spp., Veillo *parvula*, Veillo *dispar*, Veillo *rogosa*, Veillo *atypica*, *Megasphaera micronuciformis*, Atop *rimae*, Atop *parvulum*, *Filifactor alocis, Solobacterium moorei, Lachnoanaerobaculum orale, Lachnoanaerobaculum saburreum*, Ols *profusa Catonella morbi clone*, Prop *acnes, Eubacteium yurii*, Parvi *micra*
- Str *oralis* 1: Str *oralis*, Str *mitis*, Str *infantis*, Str *sanguinis*, Str *parasanguinis*, Str *australis*, Str *peroris*, Str *gordonii*, Str *salivarius*, Str *vestibularis*, Str *anginosus* group
- Str *oralis* 2: Str *oralis*, Str *mitis*, Str *infantis*, Str *australis*, Str *peroris*, Str *salivarius*, Str *vestibularis*, Str *anginosus* group
- Str *oralis* 3: Str *sanguinis*, Str *parasanguinis*, Str *gordonii*
- Mutans: Str *mutans*
- Gem *Granulicatella* Str: Gem *morbillorum*, Gem *haemolysans*, Gem *sanguinis, Granulicatella adiacens, Granulicatella elegans, Abiotrophia defectiva*
- Act spp.: Act *oris*, Act *odontolyticus*, Act *dentalis*, Act *georgiae*, Act *naeslundii*, Act spp.
- Rothia spp.: *Rothia mucilaginosa, Rothia dentocariosa, Rothia aeria, Corynebacterium* spp.
- Lact vagin: *Lactobacillus vaginalis*
- Neiss spp.: Neiss *macacae/mucosa*, Neiss *oralis*, Neiss *subflava*, Neiss *bacilliformis*, Neiss *elongata*, Neiss *flavescens*, Neiss spp, Neiss *perflava*, Neiss *cinerea*, *Lautrop mirabilis*
- Capn spp: Capn *granulosa*, Capn *gingivalis*, Capn *ochracea*, Capn *sputigena*, Capn spp.
- *HACEK:* Haem *haemolyticus*, Haem *parahaemolyticus*, Haem *parainfluenzae*, Haem *influenzae*, Cardiobact *hominis*, *Eikenella corrodens, Kingella* spp.
- *Fungi: Candida albicans*
- Faecal contaminants: Citrob *freundii*, Citrob *koseri*, Esch *coli*, Entero *asburiae*, Entero *cloacae* complex, Kleb *oxytoca*, Kleb *variicola*, Kleb *pneumoniae, Serratia marcescens*
- Black-pigmented bacteria: *Porphyromonas* spp, Prev *intermedia*, Prev *nigrescens*, Prev *histicola*, Prev *melaninogenica*, Prev *loescheii, Prevotella* spp
- Not pigmented Bact group: nipig Bact sp, Prev *salivae*
- Fuso spp: Fuso *nucleatum*, Fuso *periodontium*
- C spp.: C *rectus*, C *concisus*, C *showae*, C spp
- *Selenomonas* spp.: *Selenomonas* spp.
- Gram-positive aerobic cocci: Str *oralis*, Str *mitis*, Str *infantis*, Str *sanguinis*, Str *parasanguinis*, Str *australis*, Str *peroris*, Str *gordonii*, Str *salivarius*, Str *vestibularis*, Str *anginosus* group, Strep *mutans*, Gem *morbillorum*, Gem *haemolysans*, Gem *sanguinis*, *Granulicatella adiacens, Granulicatella elegans, Abiotrophia defectiva*

- Gram-positive aerobic rods: Act *oris*, Act *odontolyticus*, Act *dentalis*, Act *georgiae*, Act *naeslundii*, Act spp., *Rothia mucilaginosa, Rothia dentocariosa, Rothia aeria, Corynebacterium* spp., Lact vagin
- Gram-negative aerobic cocci: Neiss *macacae/mucosa*, Neiss *oralis*, Neiss *subflava*, Neiss *bacilliformis*, Neiss *elongata*, Neiss *flavescens*, Neiss spp, Neiss *perflava*, Neiss *cinerea*, *Lautrop mirabilis*
- Gram-negative aerobic rods: Capn *granulosa*, Capn *gingivalis*, Capn *ochracea*, Capn *sputigena*, Capn spp., Haem *haemolyticus*, Haem *parahaemolyticus*, Haem *parainfluenzae*, Haem *influenzae*, *Cardiobact hominis, Eikenella corrodens, Kingella* spp
- Gram-positive anaerobic cocci: Parvi *micra*
- Gram-positive anaerobic rods: Atop *rimae*, Atop *parvulum*, *Filifactor alocis, Solobacterium moorei, Lachnoanaerobaculum orale Lachnoanaerobaculum saburreum*, Ols *profusa, Catonella morbi clone*, Prop *acnes, Eubacteium yurii*
- Gram-negative anaerobe cocci: Veillo *parvula*, Veillo *dispar*, Veillo *rogosa*, Veillo *atypica, Megasphaera micronuciformis*
- Gram-negative anaerobic rods: *Porphyromonas* spp., Prev *intermedia*, Prev *nigrescens*, Prev *histicola*, Prev *melaninogenica,* Prev *loescheii*, Prev spp, nipig Bact spp, Prev *salivae*, Fuso *nucleatum*, Fuso *periodontium*, C *rectus*, C *concisus*, C *showae*, C spp, *Selenomonas* spp.

Computation to the expected absolute difference of two randomly chosen observations:
To compute the expected absolute difference of two randomly chosen observations Y_1 and Y_2, we use the half normal distribution with mean value $\frac{\sqrt{2}}{\sqrt{\pi}}\sigma$ and variance $Var(Y_1 - Y_2) = {\sigma_{Y_1}}^2 + {\sigma_{Y_2}}^2 = 2\sigma^2$. This results in $E[|Y_1 - Y_2|] = \mu = \frac{\sqrt{2}}{\sqrt{\pi}}\sigma_{diff} = \frac{\sqrt{2}}{\sqrt{\pi}}\sqrt{2}\sigma = \frac{2}{\sqrt{\pi}}\sigma = 1.13\sigma$

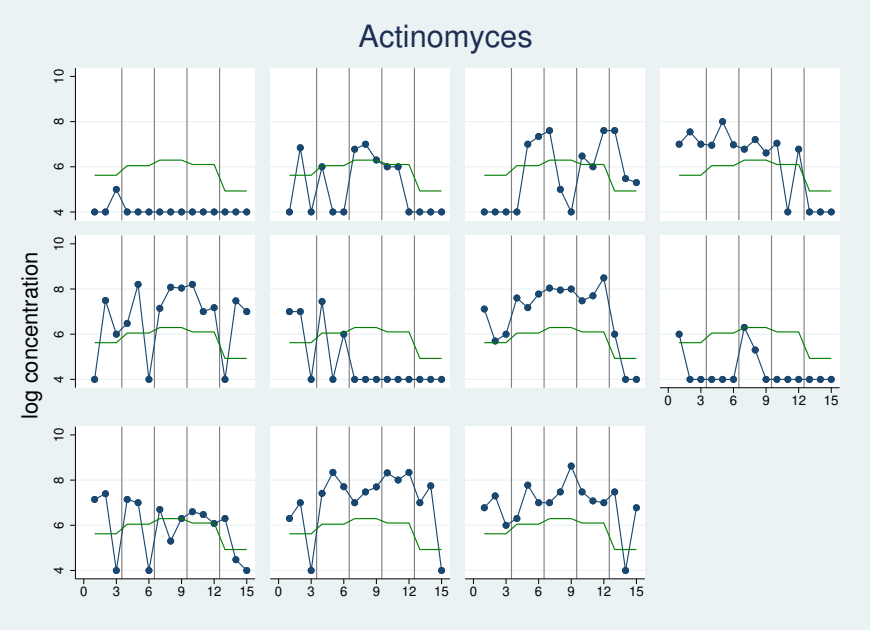

Figure 8 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Actinomyces* for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

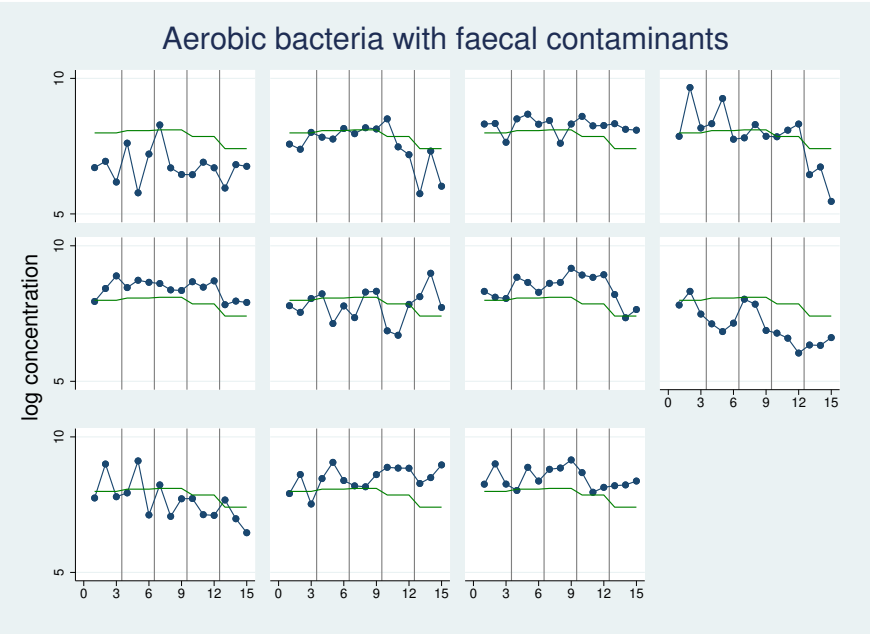

Figure 9 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Aerobic bacteria wfc for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

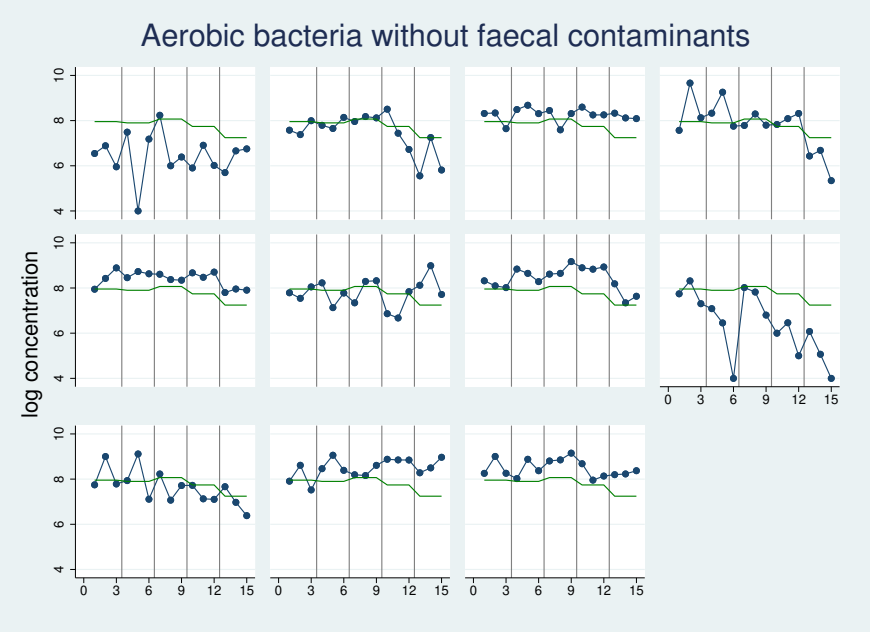

Figure 10 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Aerobic bacteria fce for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

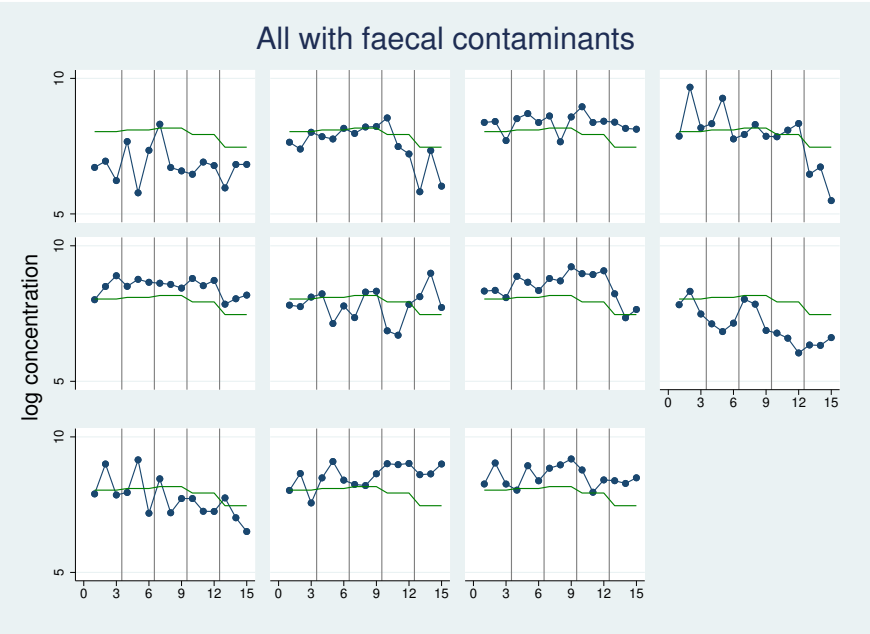

Figure 11 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of All wfc for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

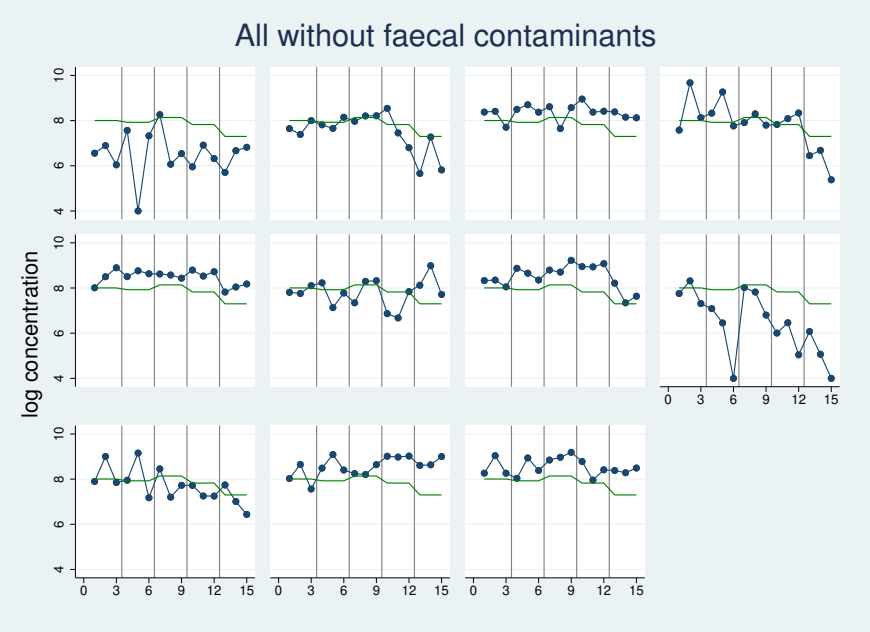

Figure 12 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of All fce for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

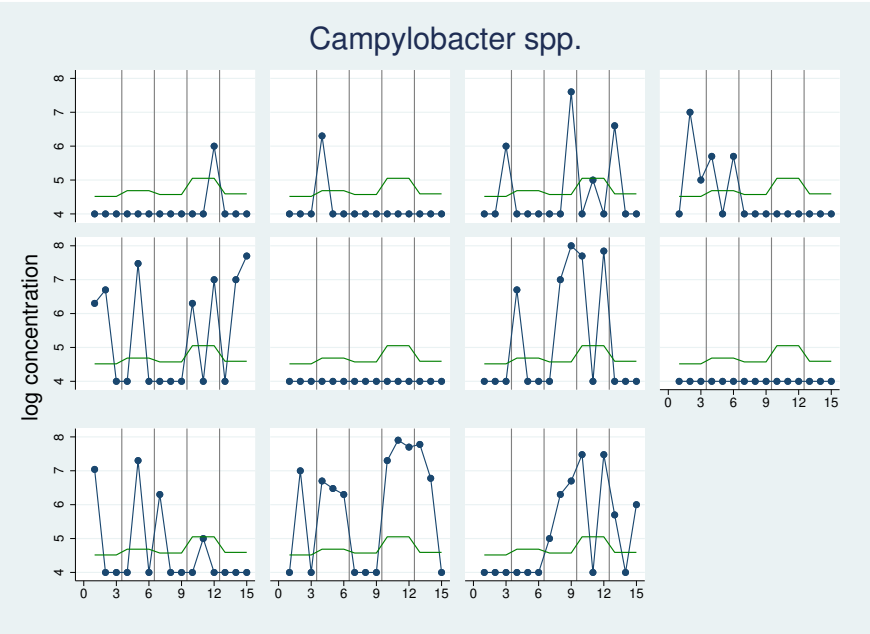

Figure 13 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Campylobacter* spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

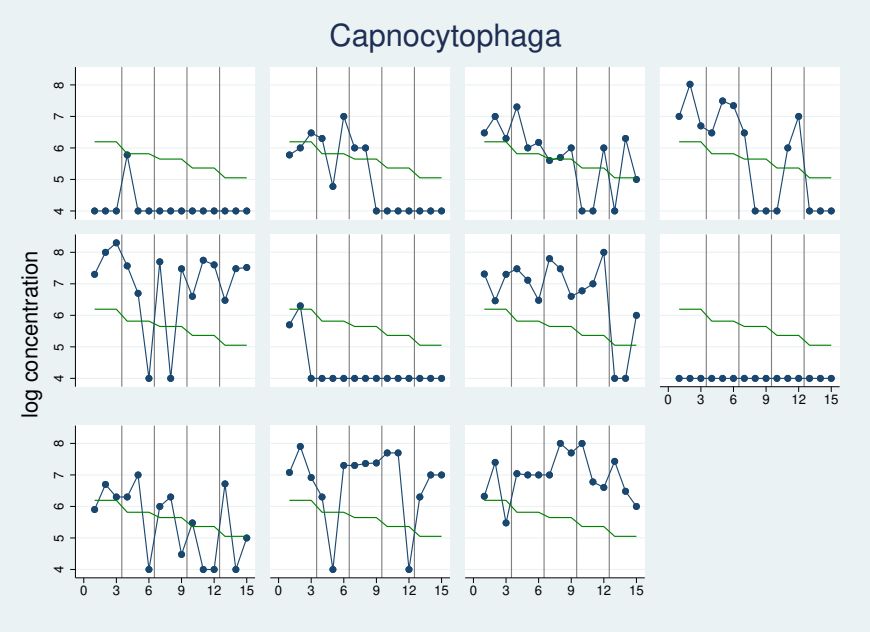

Figure 14 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Capnocytophaga* for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

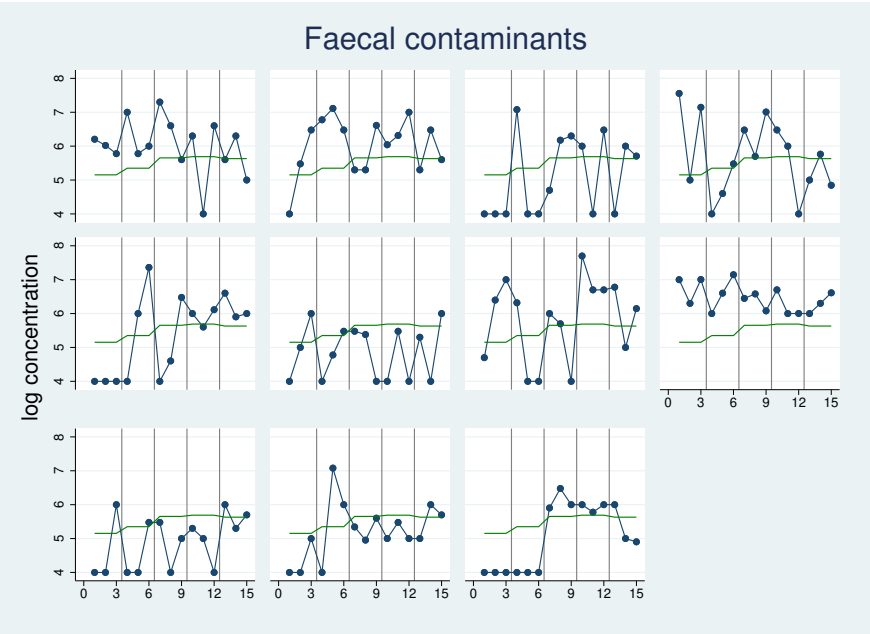

Figure 15 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Faecal contaminants for each of the 11 participantsover the 5 phases. Green line: mean value per phase, grey line: end of the phase.

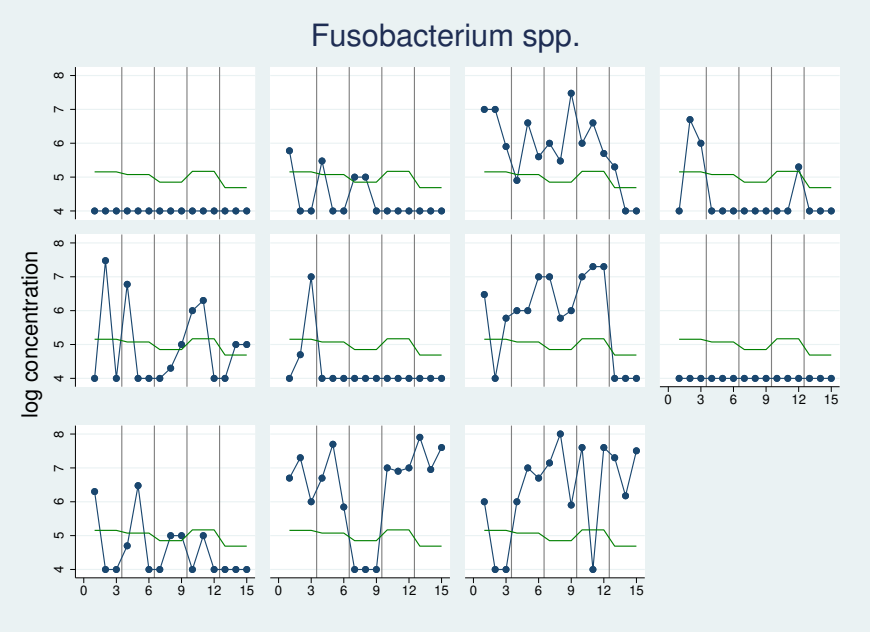

Figure 16 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Fusobacterium* spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

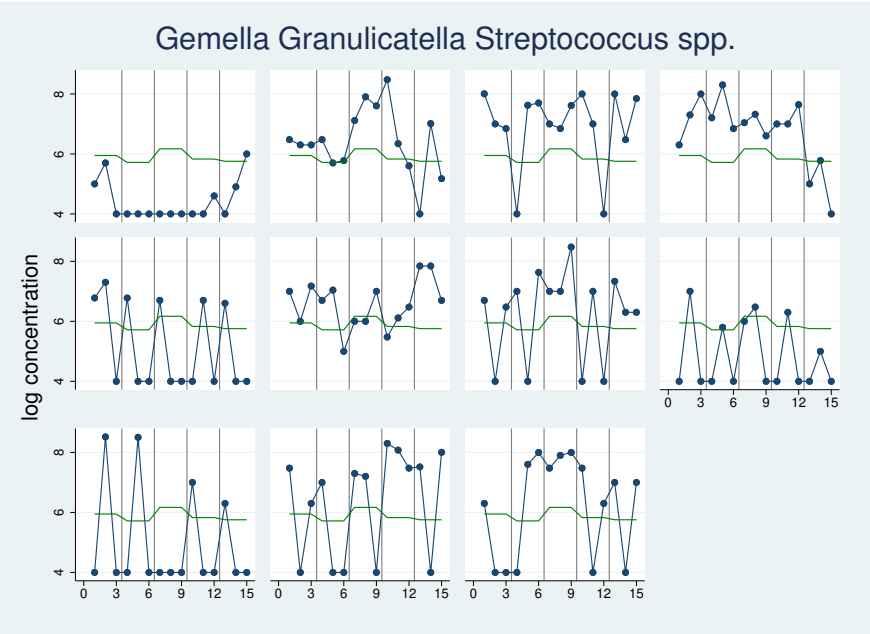

Figure 17 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Gemella Granulicatella Streptococcus* spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

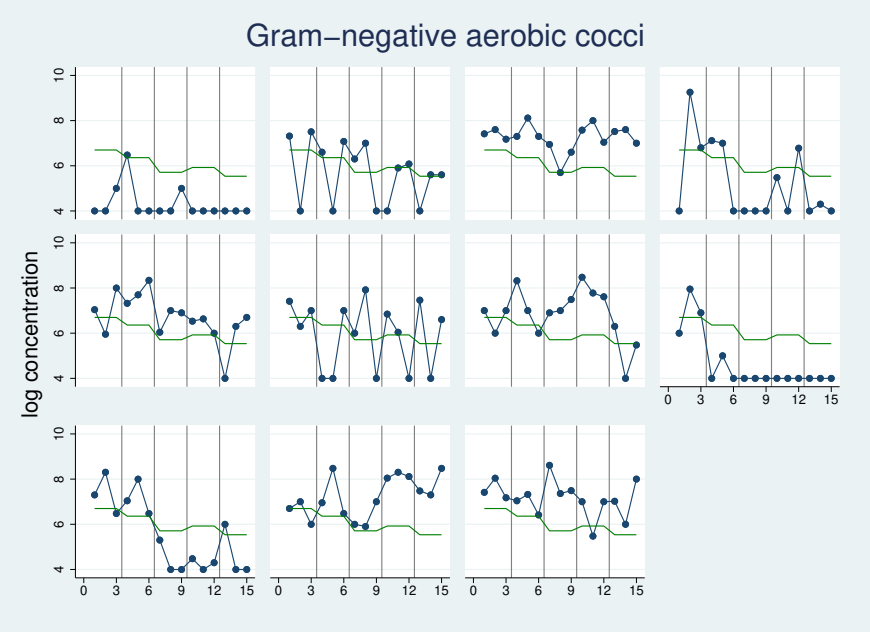

Figure 18 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative aerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

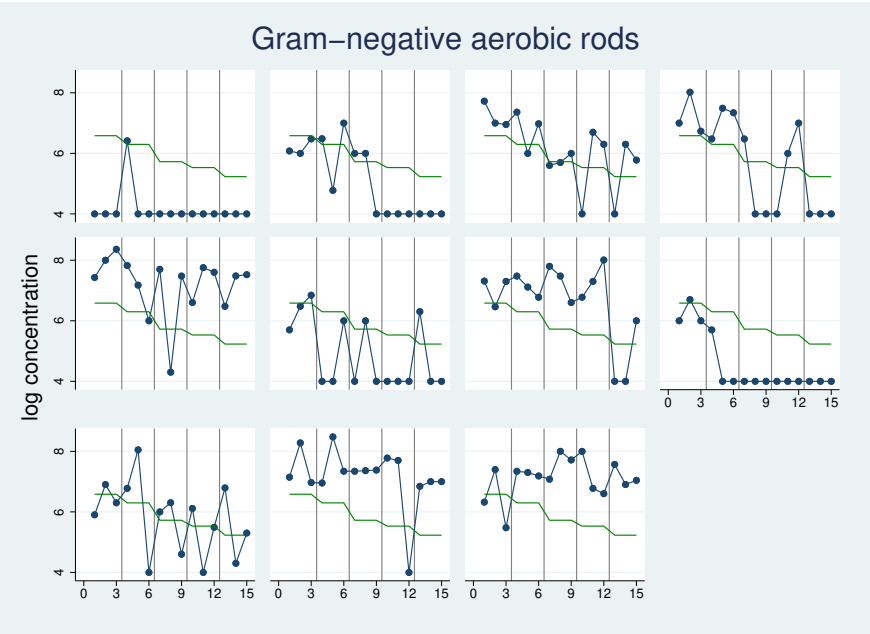

Figure 19 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative aerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

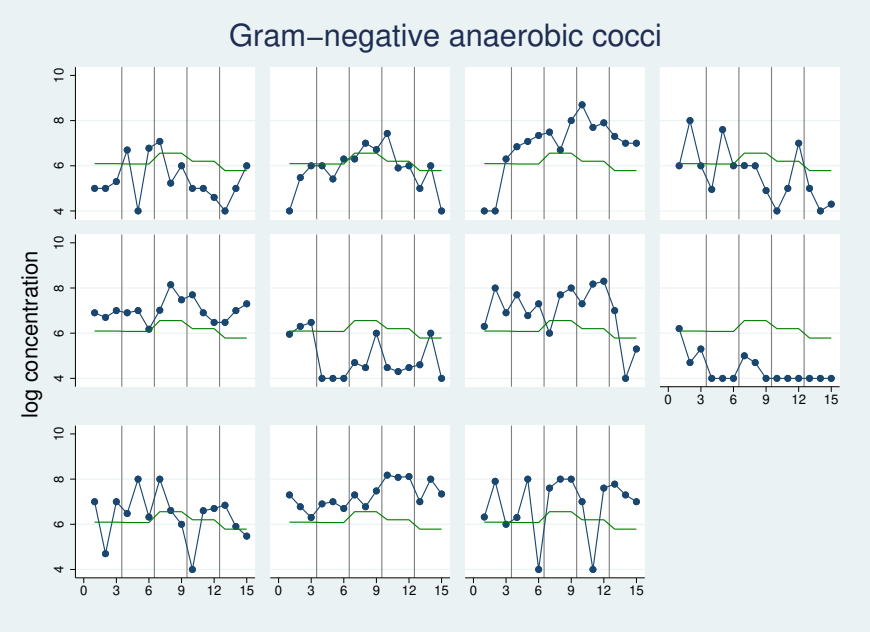

Figure 20 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative anaerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

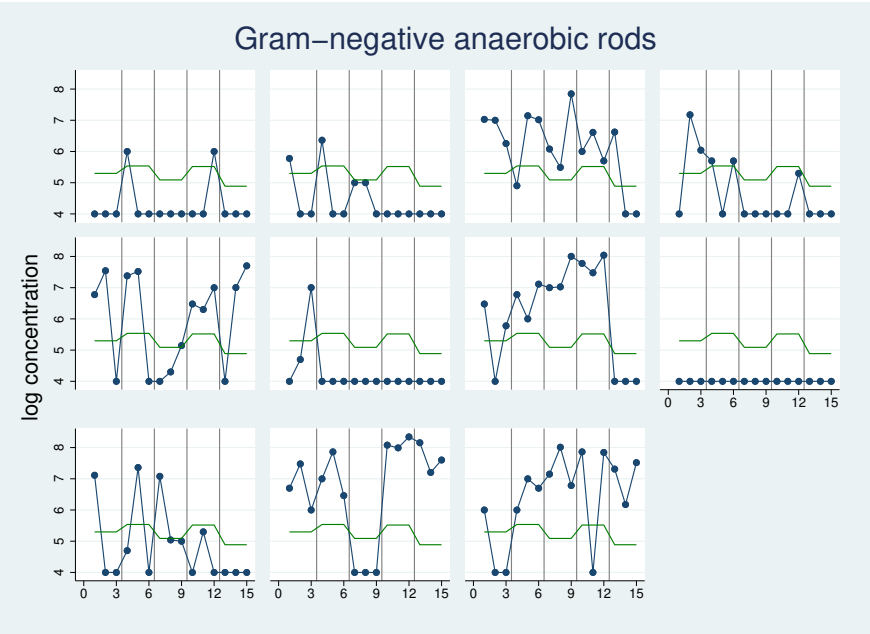

Figure 21 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative anaerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

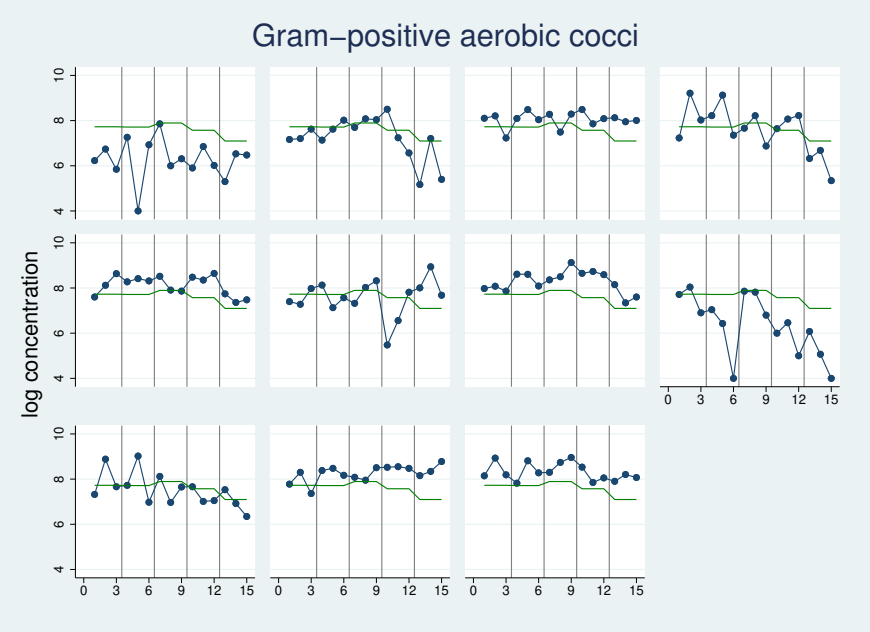

Figure 22 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-positive aerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

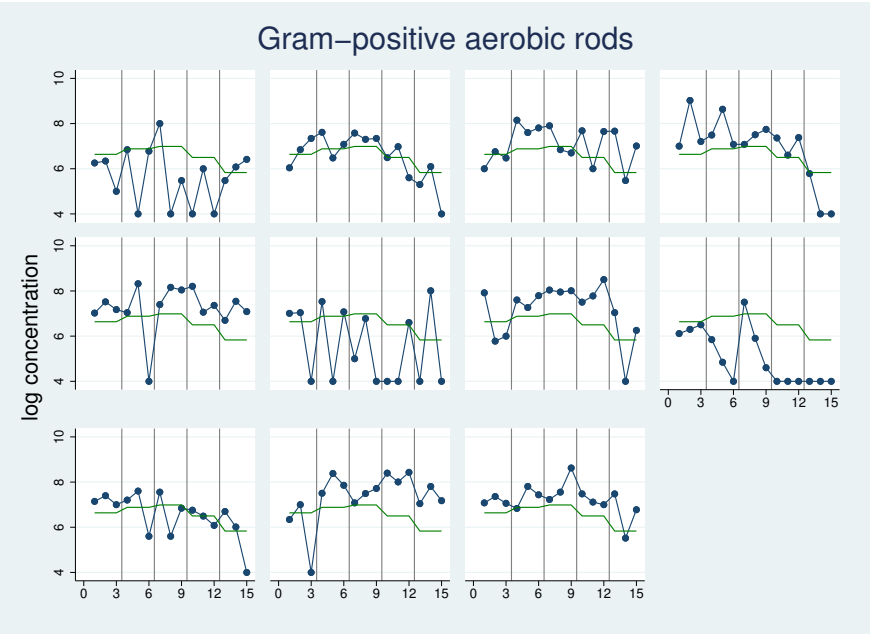

Figure 23 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-positive aerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

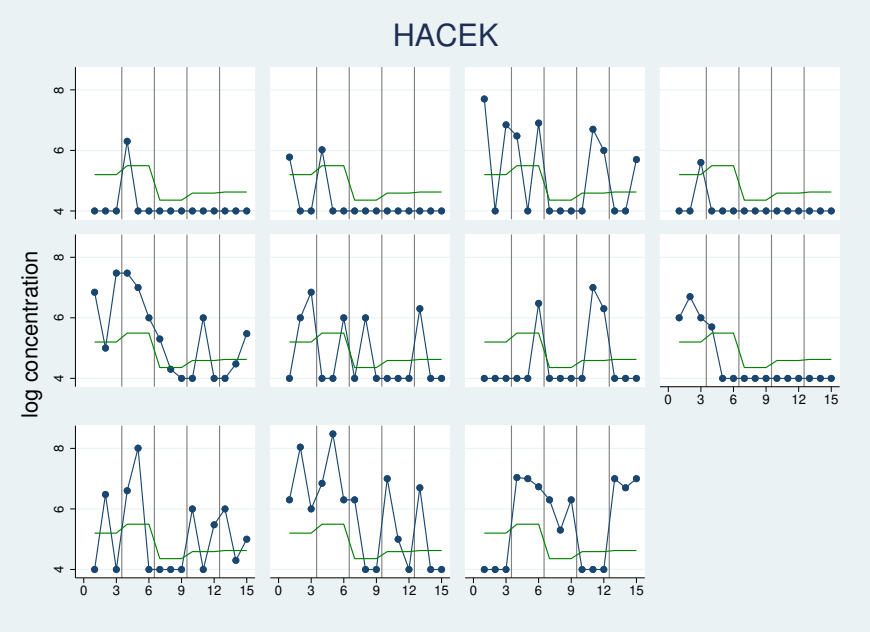

Figure 24 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Hacek for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

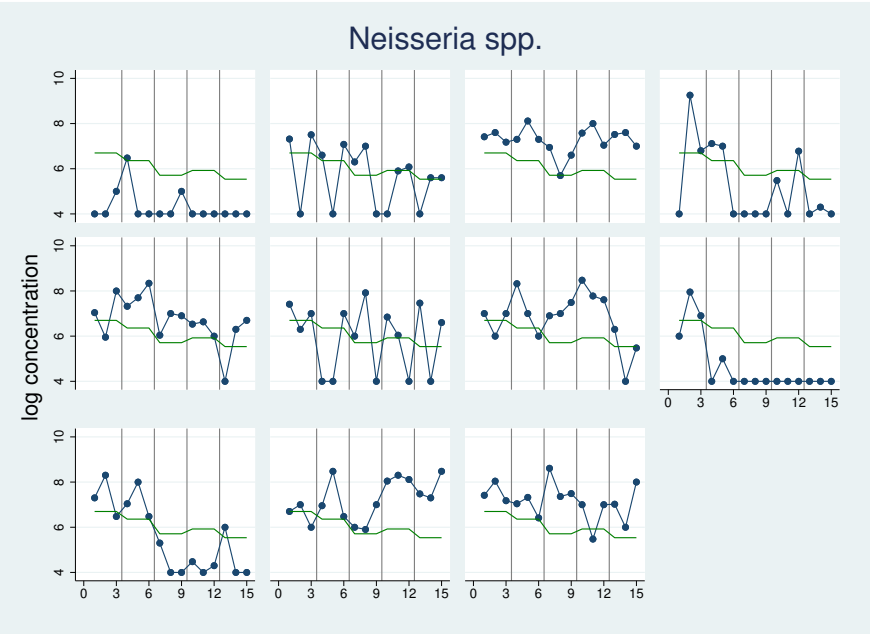

Figure 25 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Neisseria* spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

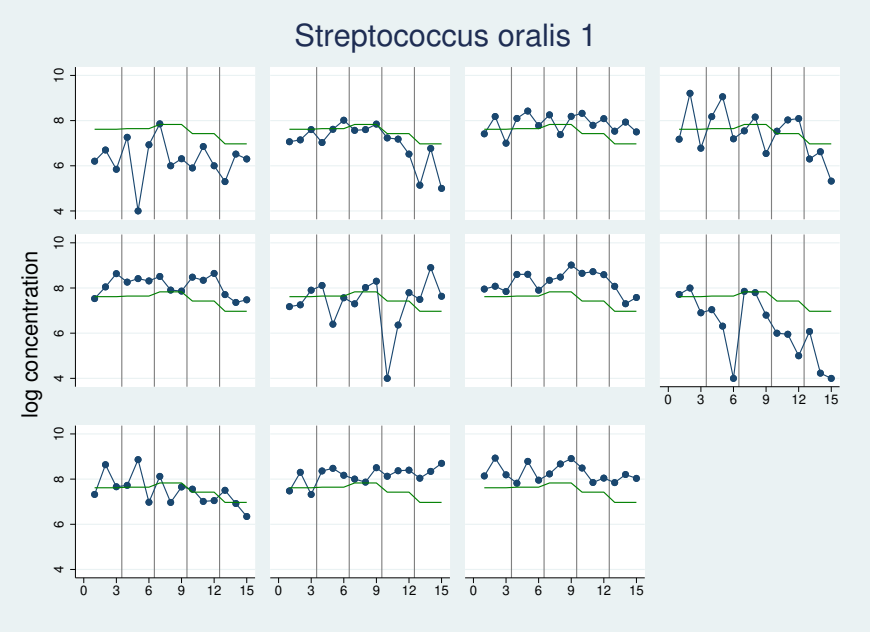

Figure 26 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Streptococcus oralis* 1 for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

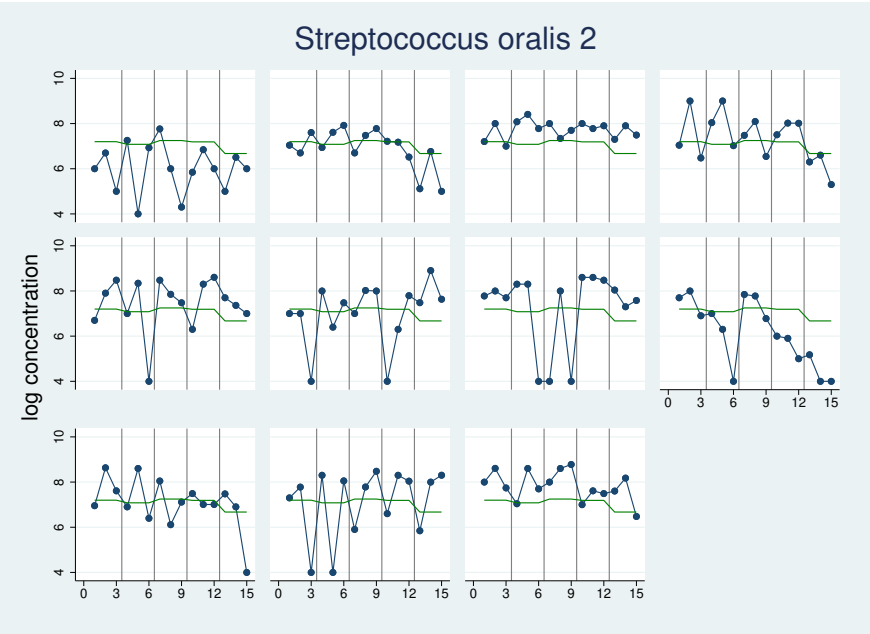

Figure 27 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Streptococcus oralis* 2 for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

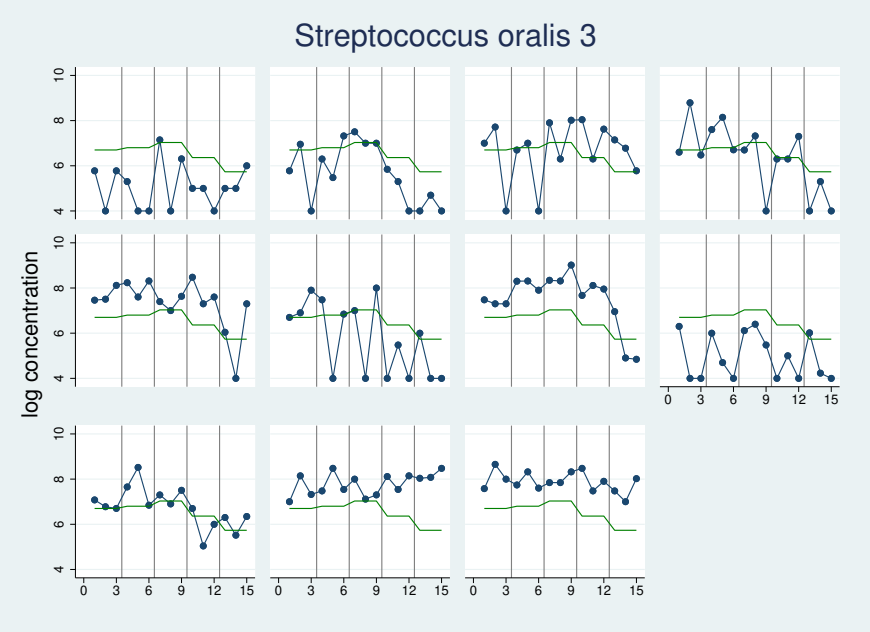

Figure 28 Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of *Streptococcus oralis* 3 for each of the 11 participantsover the 5 phases. Green line: mean value per phase, grey line: end of the phase.

Figures

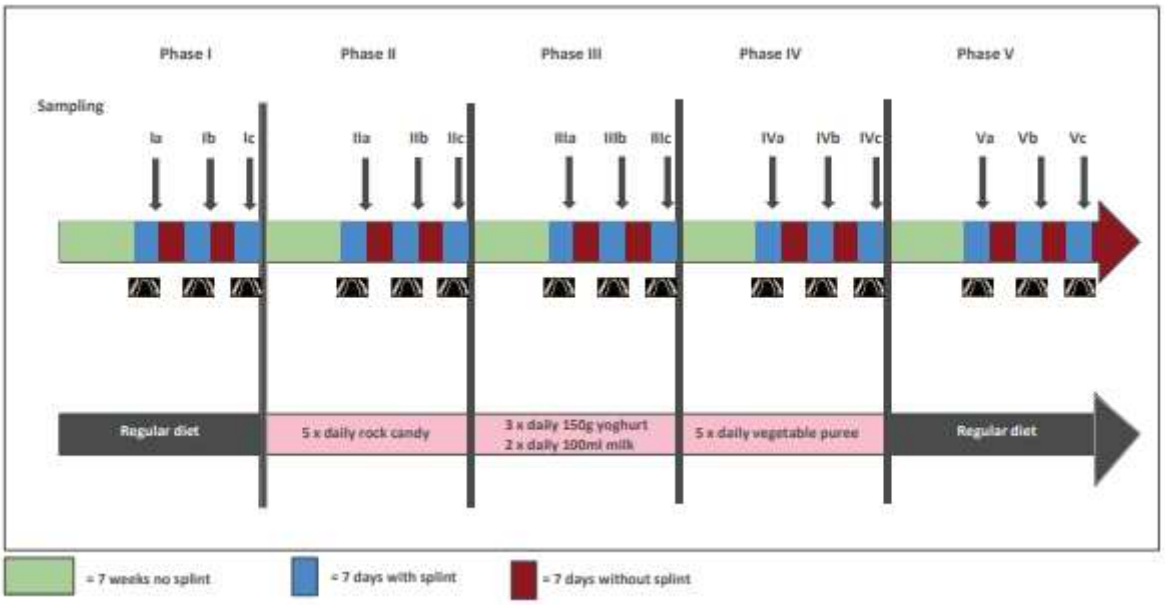

Figure 1

Study design: Description of the sampling and nutrition during the five phases.

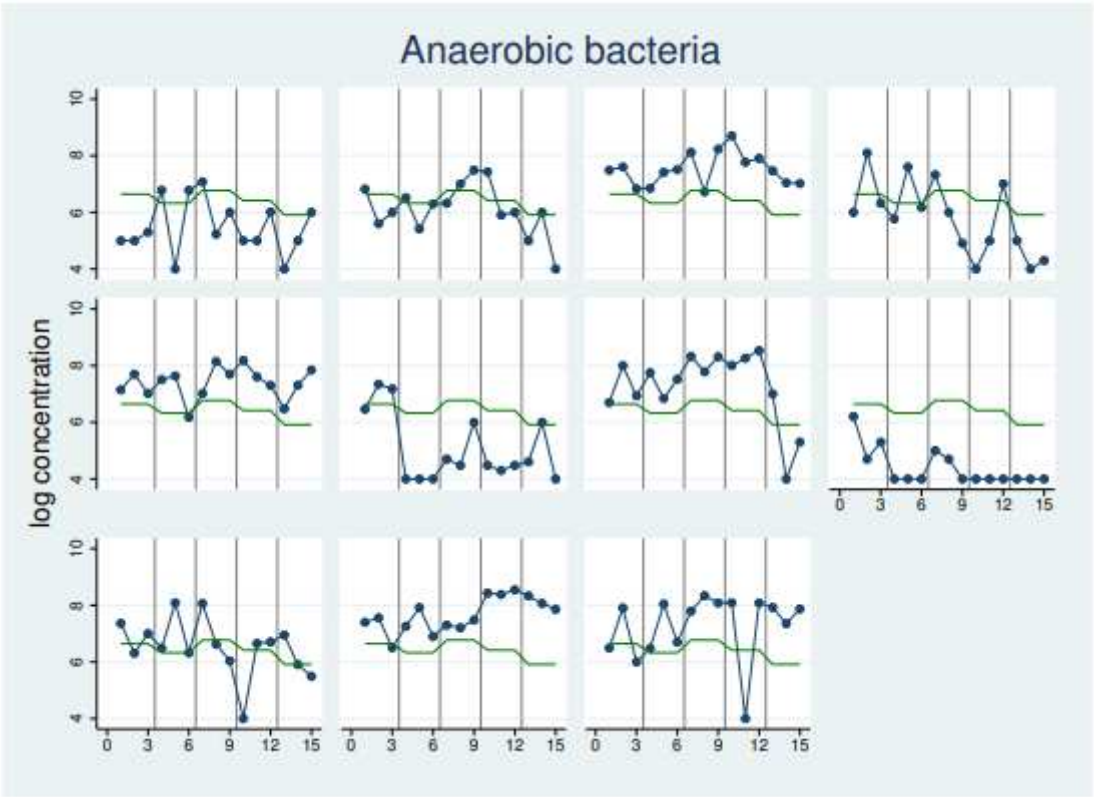

Figure 2

Example scatter plot of individual bacterial concentrations over time. Concentrations (in log-10 CFU per ml) of anaerobic bacteria for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

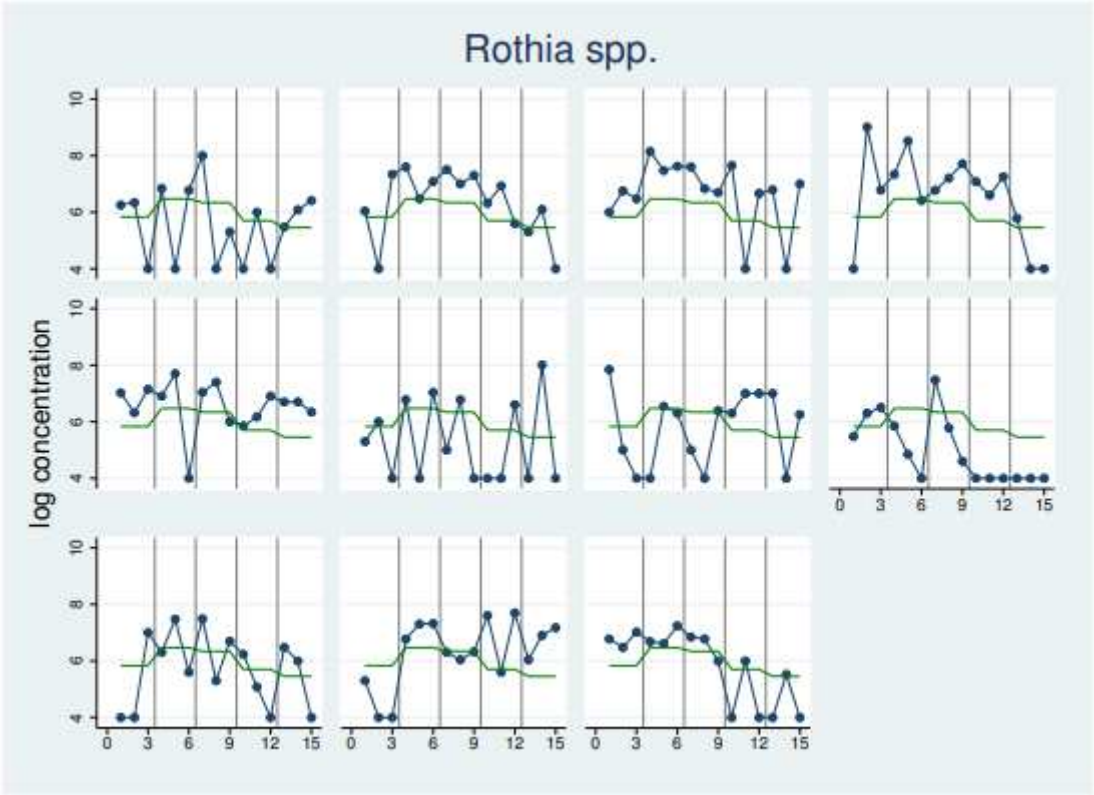

Figure 3

Example scatter plot of individual bacterial concentrations over time. Concentrations (in log-10 CFU per ml) of Rothia spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

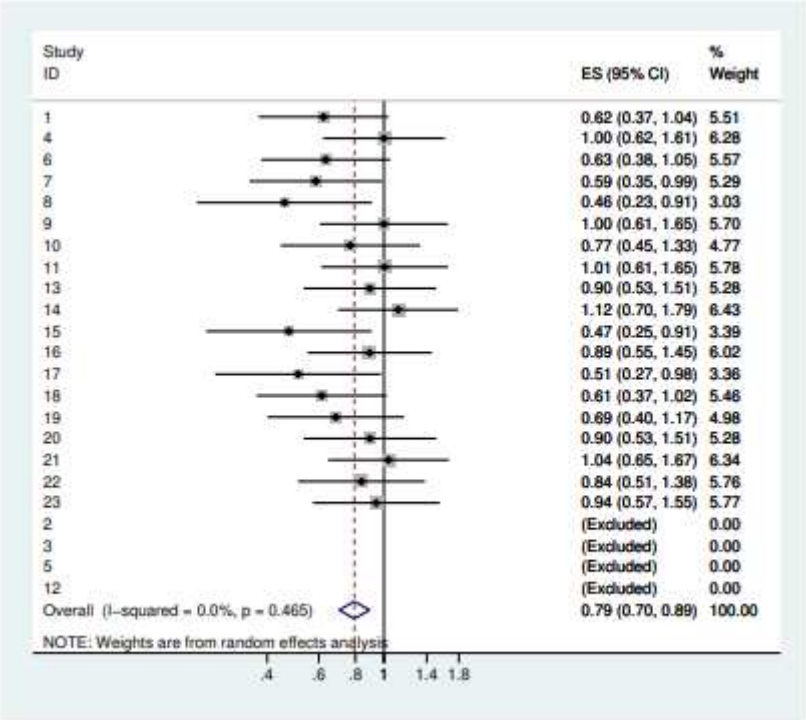

Figure 4

Meta-analysis of the standard deviations of the initial values. Each study represents one bacterial category.

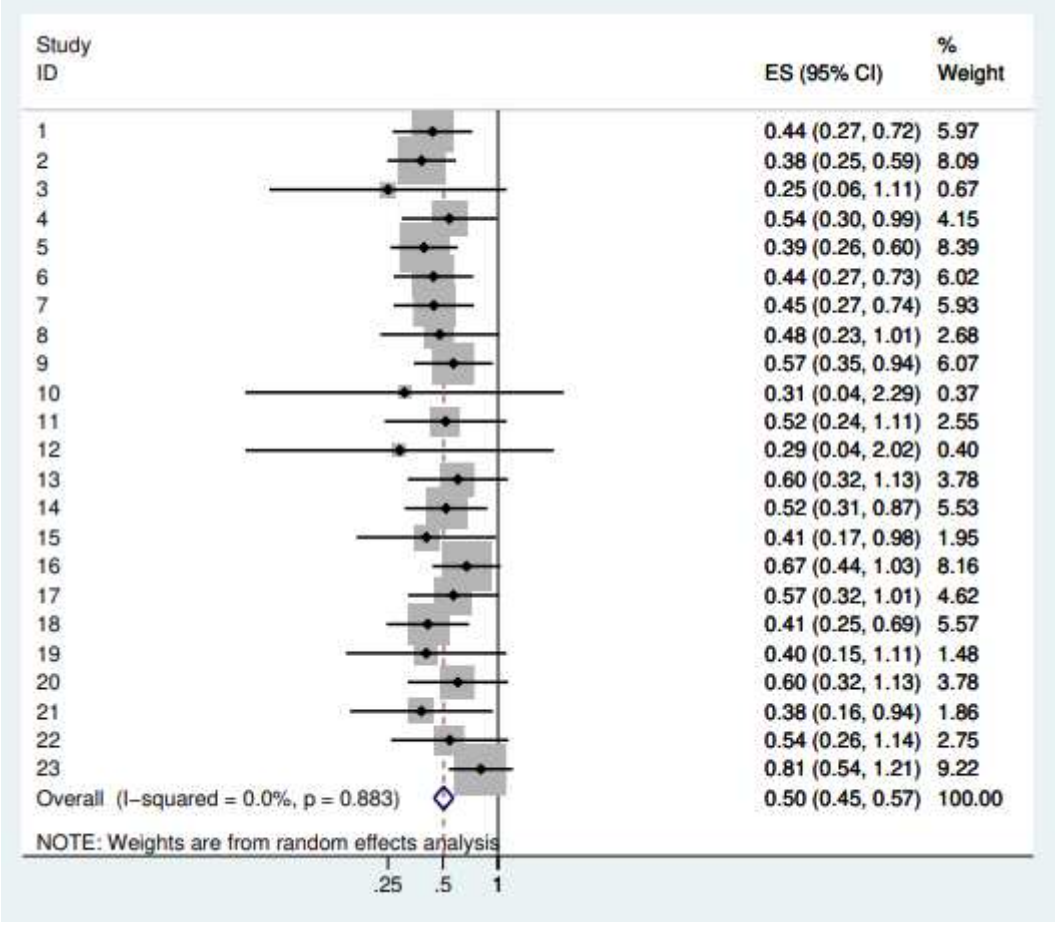

Figure 5

Meta-analysis of the standard deviations of the increments. Each study represents one bacterial category

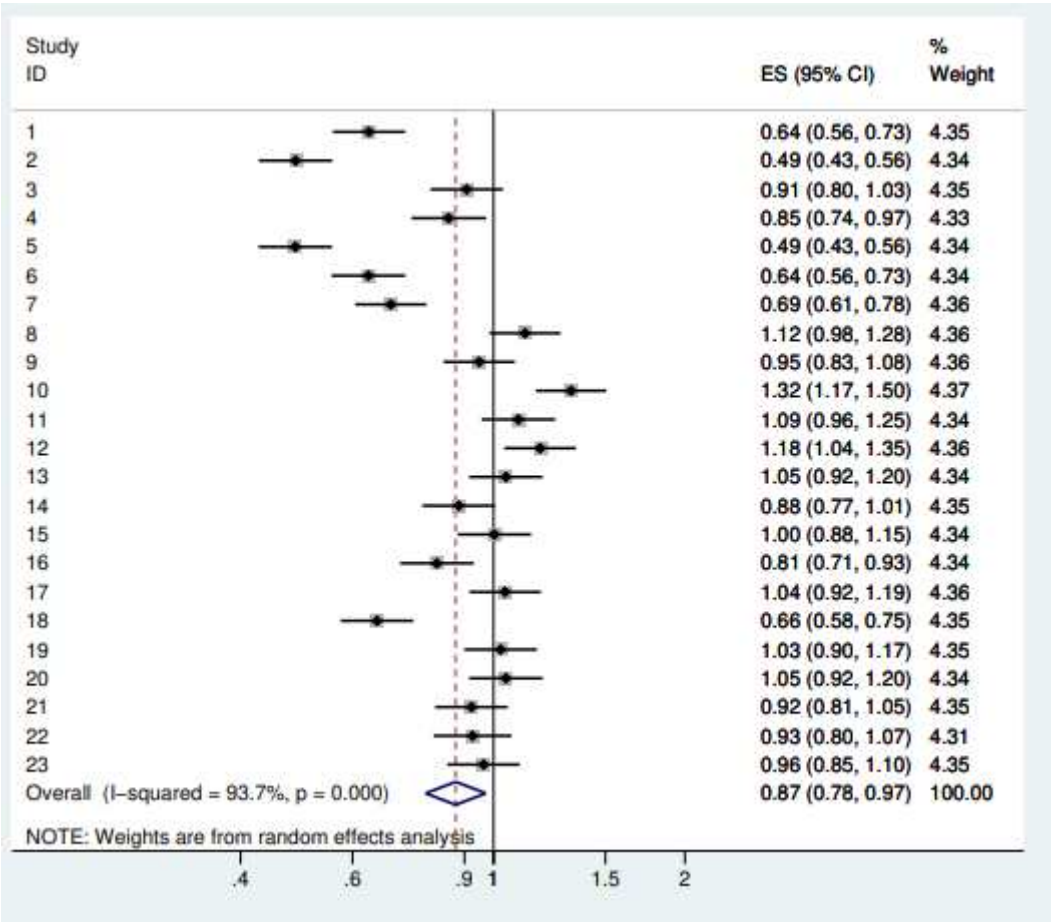

Figure 6

Meta-analysis of the standard deviations of the residuals. Each study represents one bacterial category.

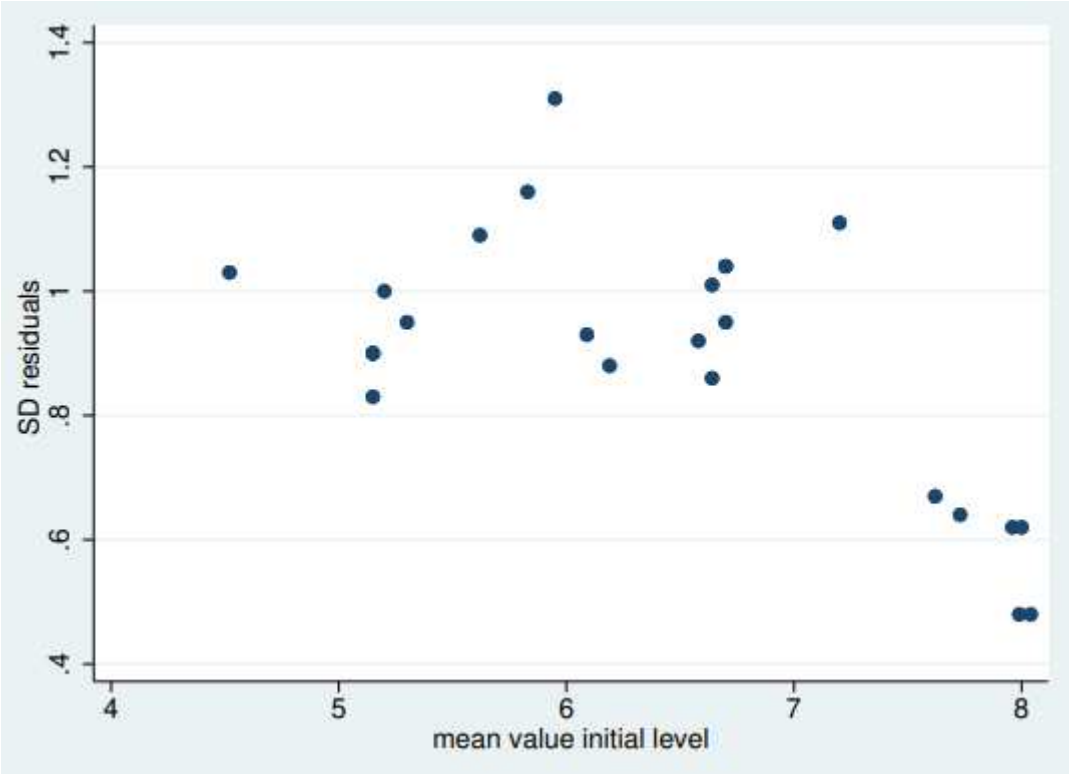

Figure 7

Mean value of initial value and standard deviation of the residuals.

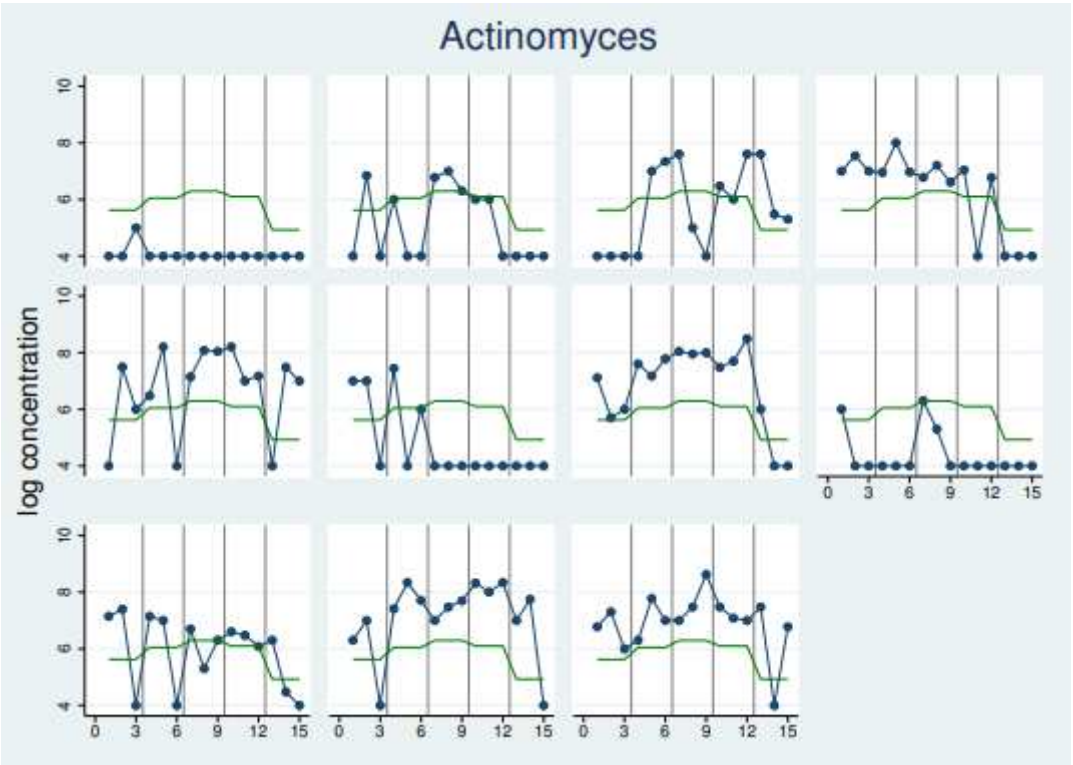

Figure 8

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Actinomyces for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

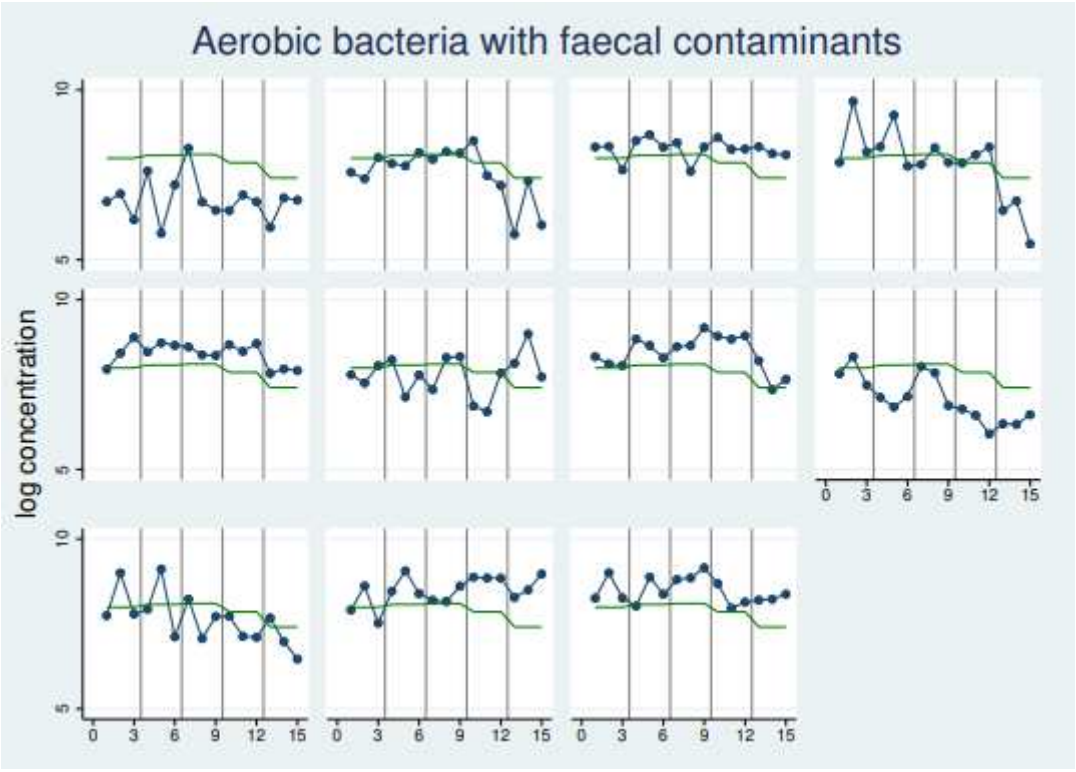

Figure 9

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Aerobic bacteria wfc for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

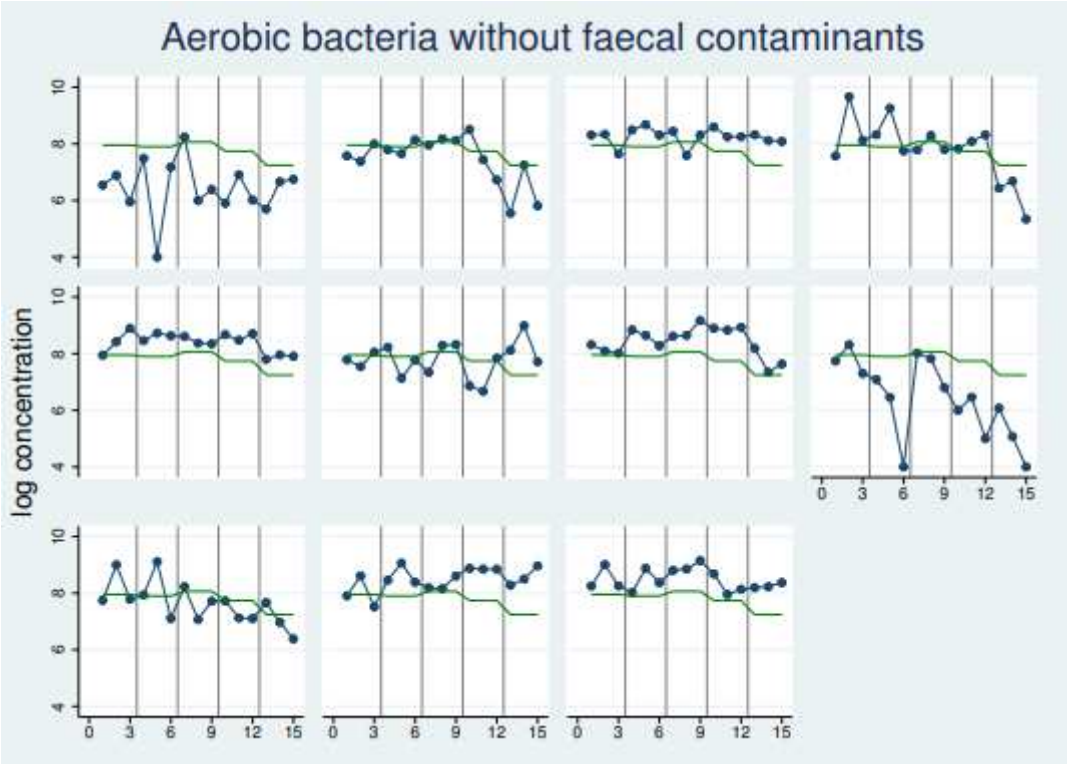

Figure 10

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Aerobic bacteria fce for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

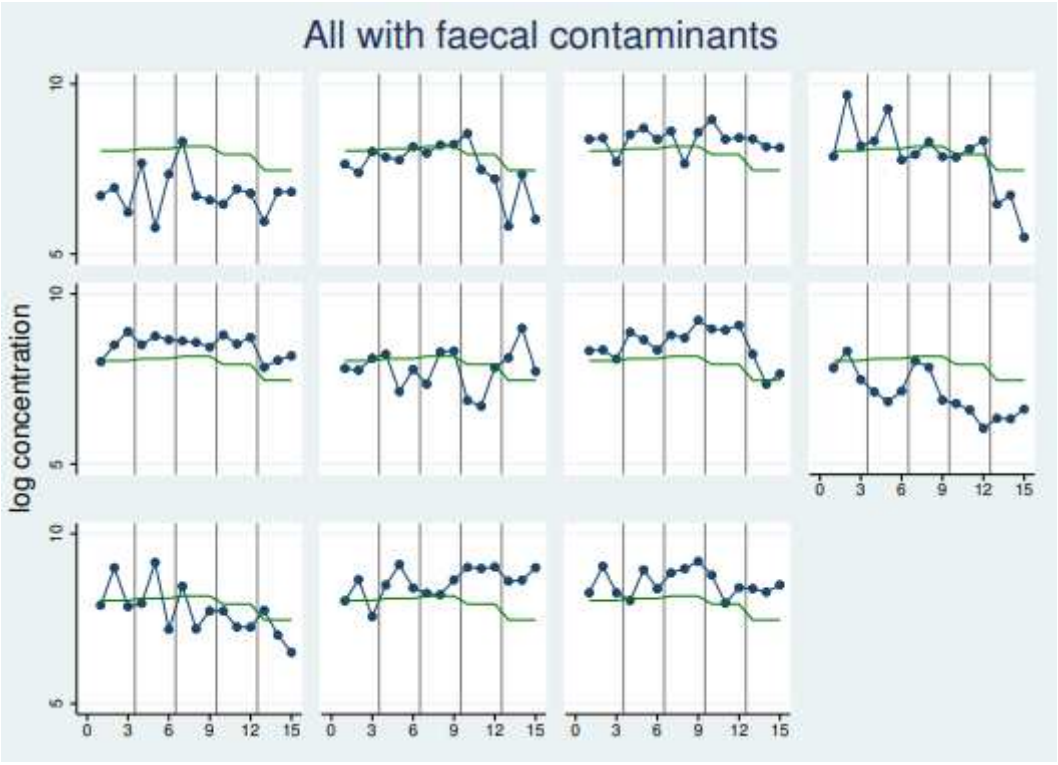

Figure 11

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of All wfc for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

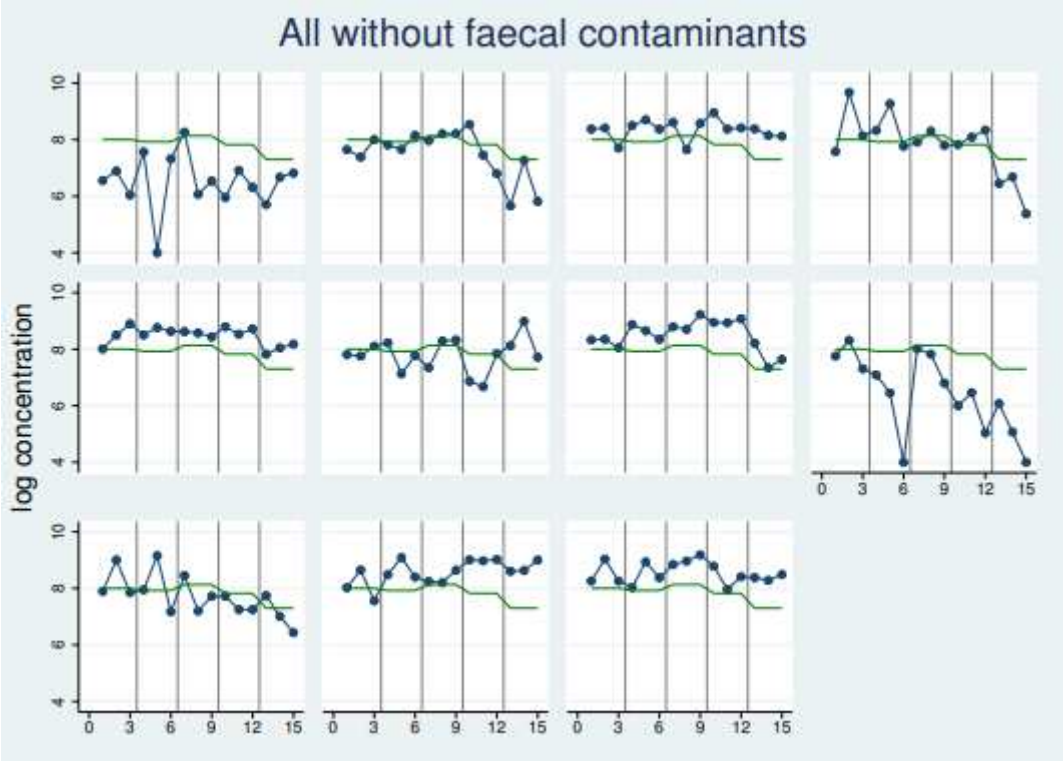

Figure 12

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of All fce for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

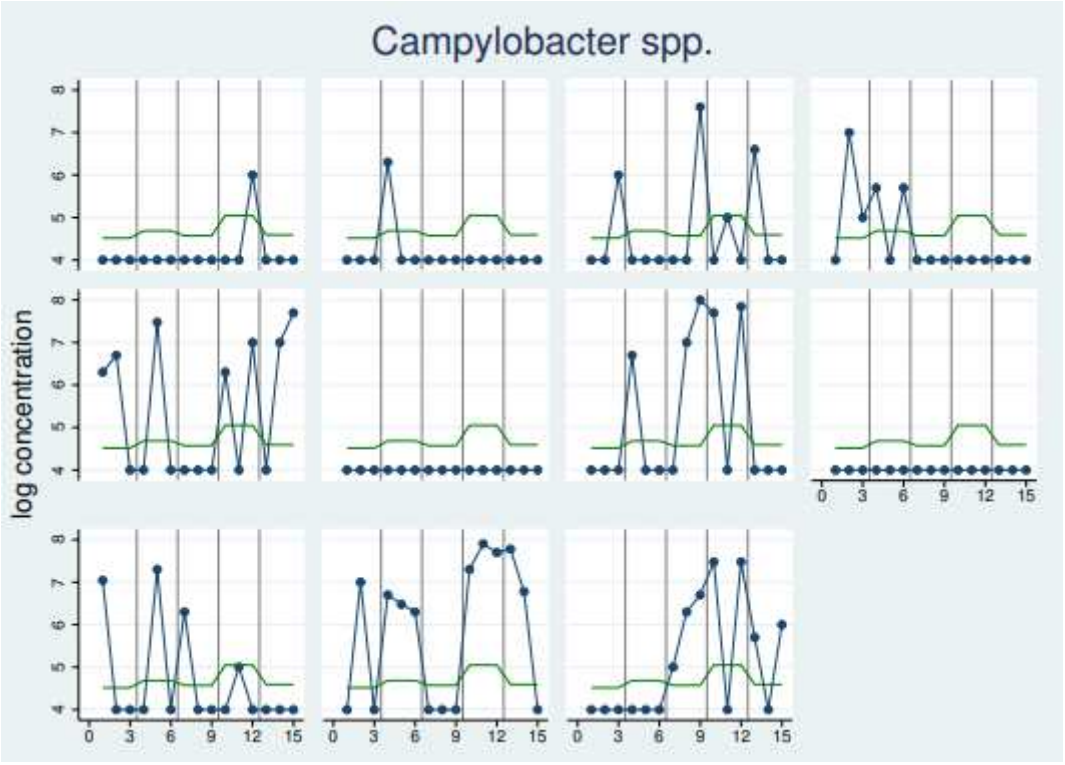

Figure 13

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Campylobacter spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

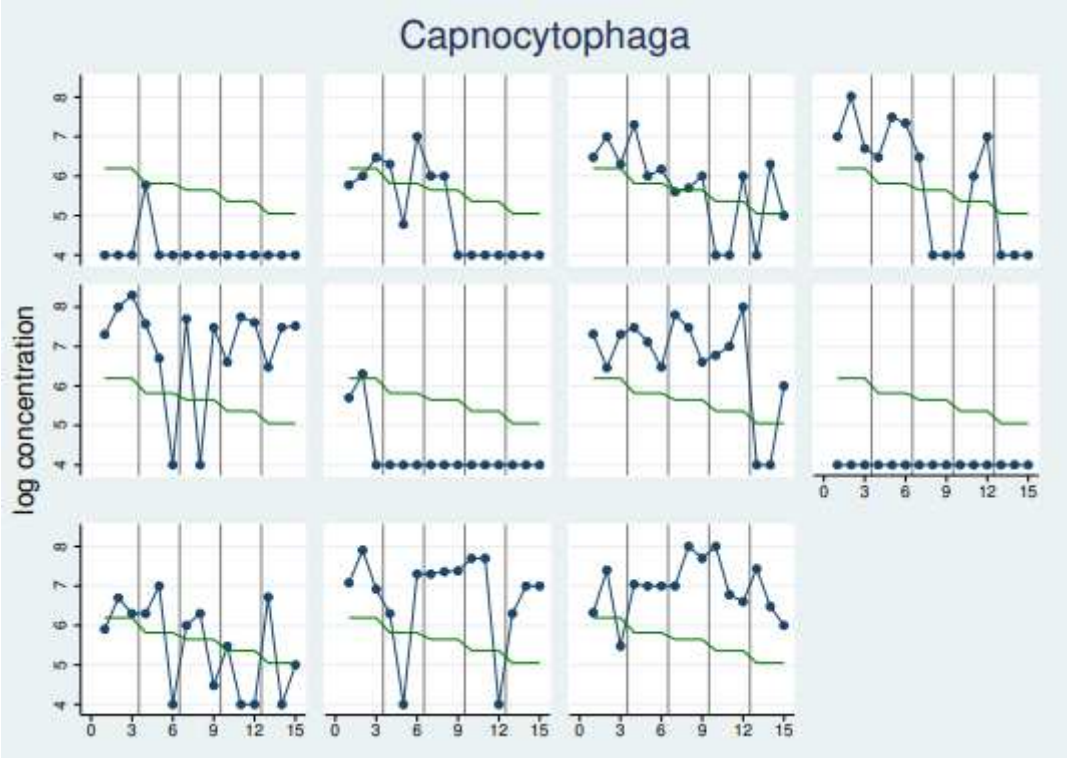

Figure 14

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Capnocytophaga for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

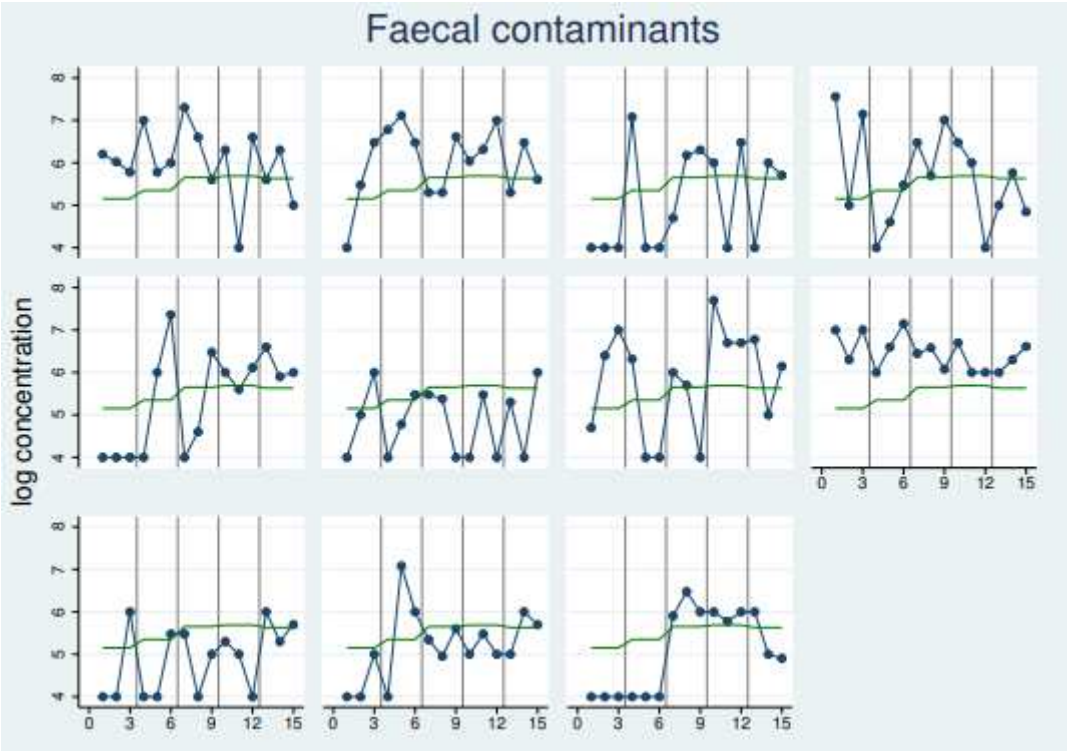

Figure 15

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Faecal contaminants for each of the 11 participantsover the 5 phases. Green line: mean value per phase, grey line: end of the phase.

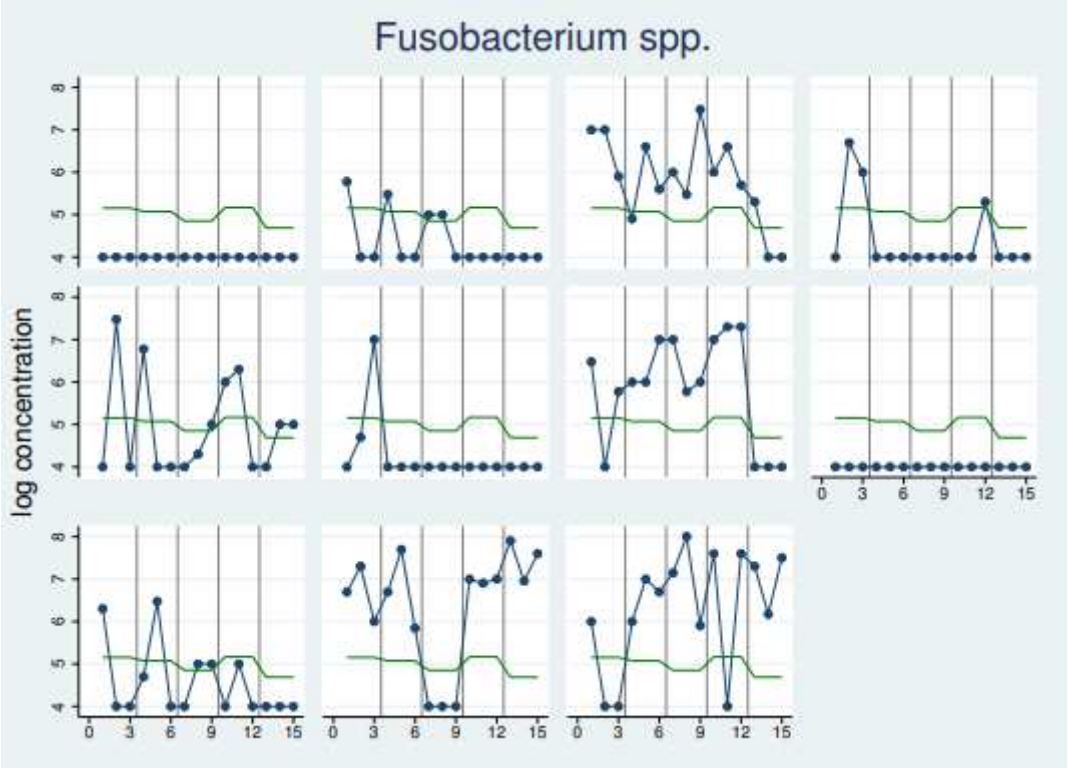

Figure 16

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Fusobacterium spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

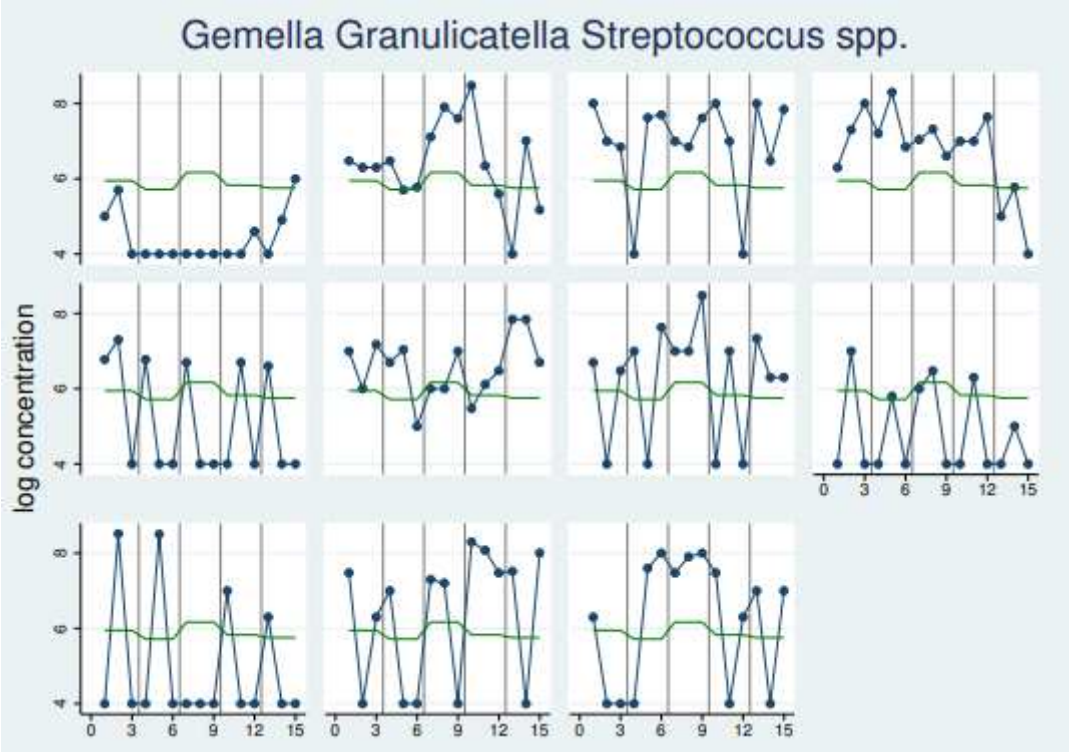

Figure 17

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gemella Granulicatella Streptococcus spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

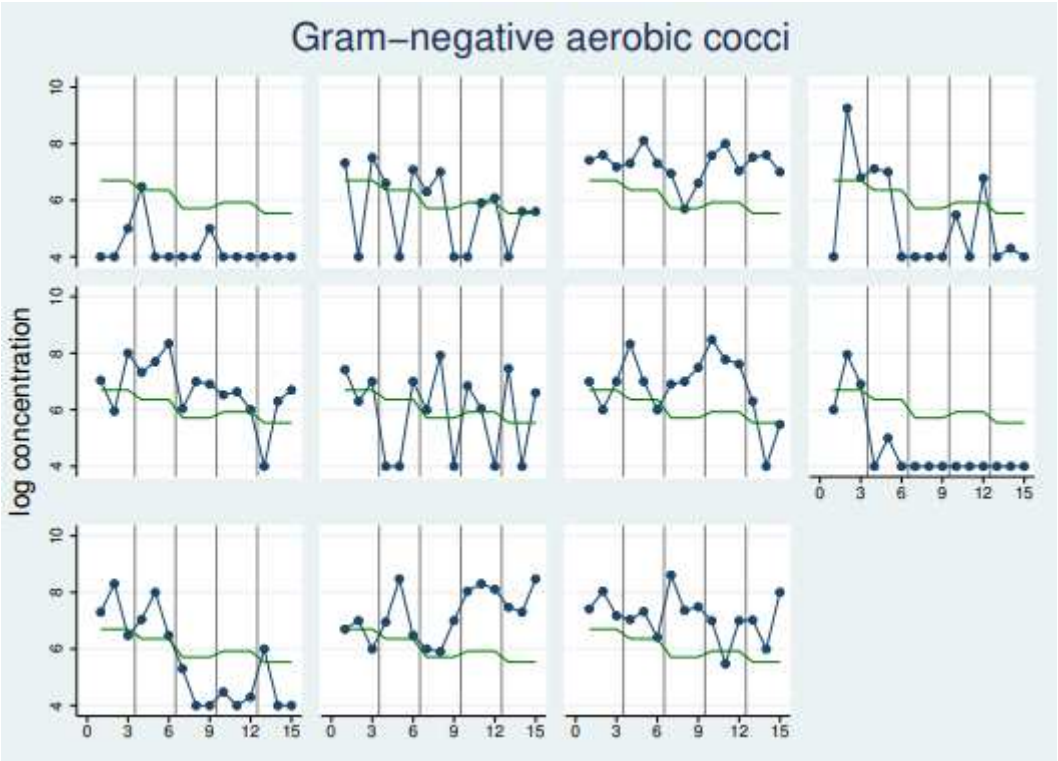

Figure 18

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative aerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

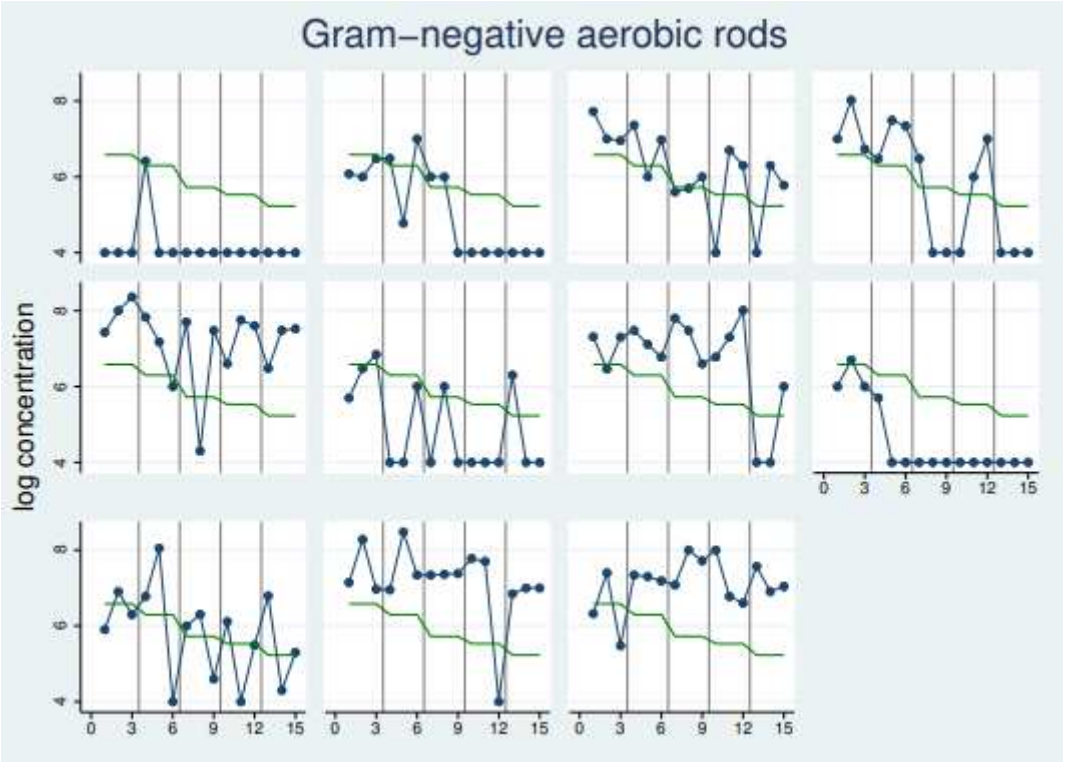

Figure 19

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative aerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

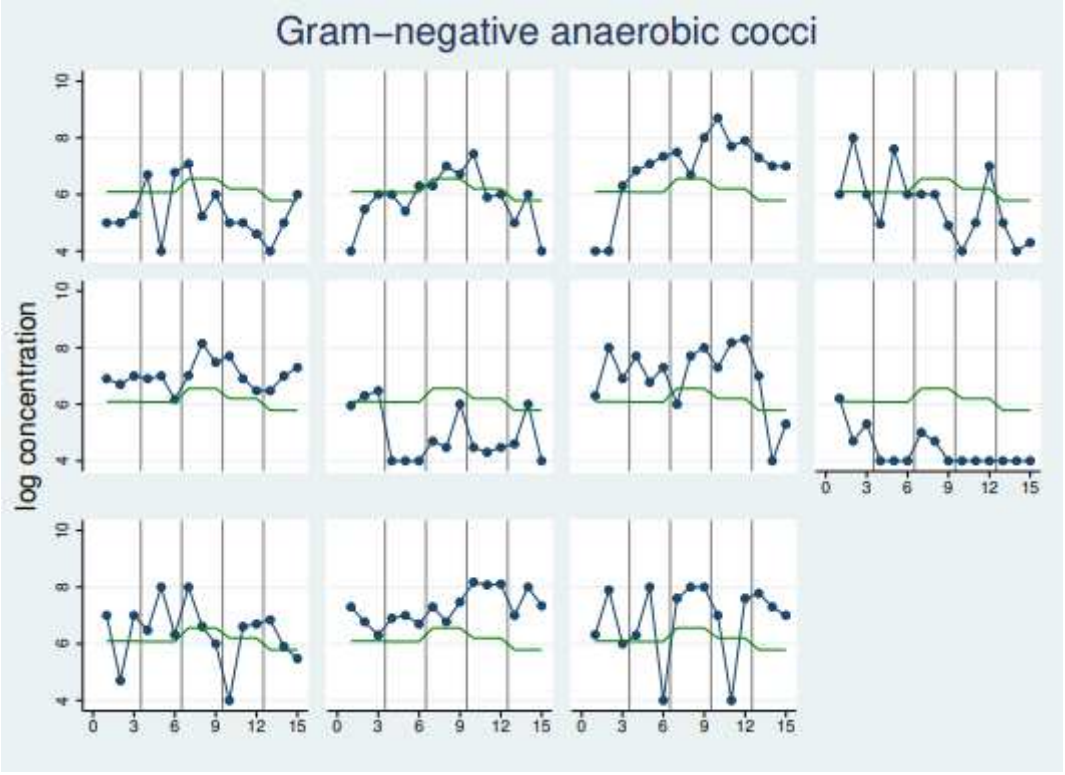

Figure 20

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative anaerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

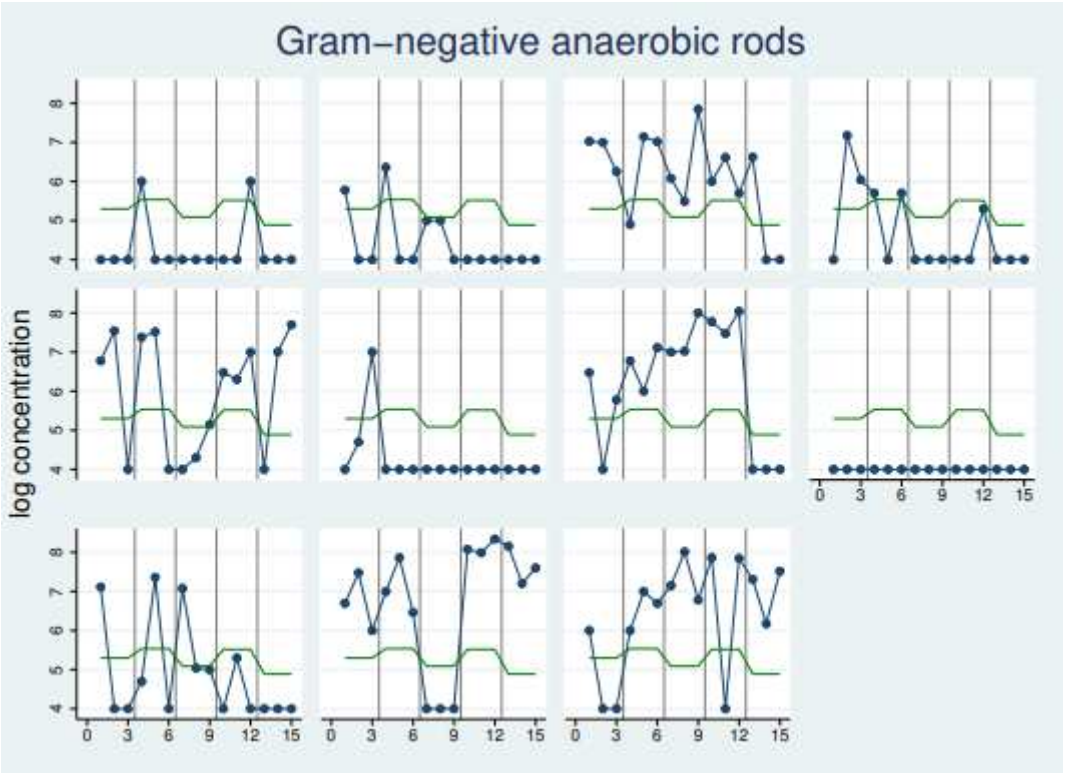

Figure 21

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-negative anaerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

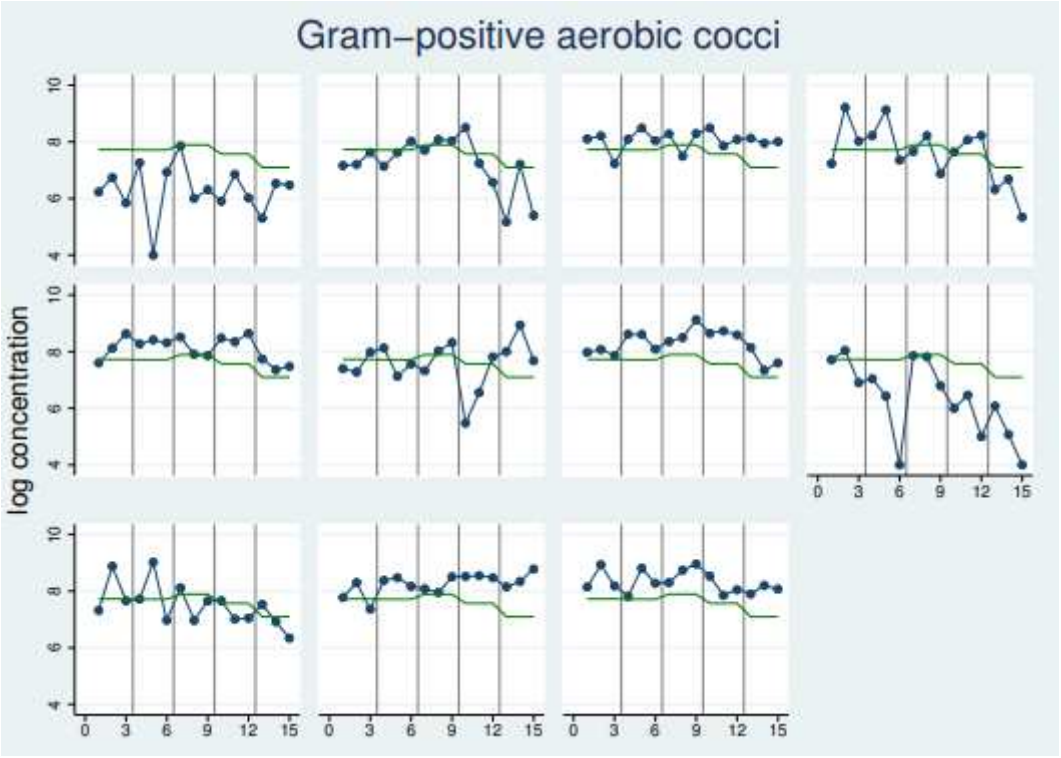

Figure 22

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-positive aerobic cocci for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

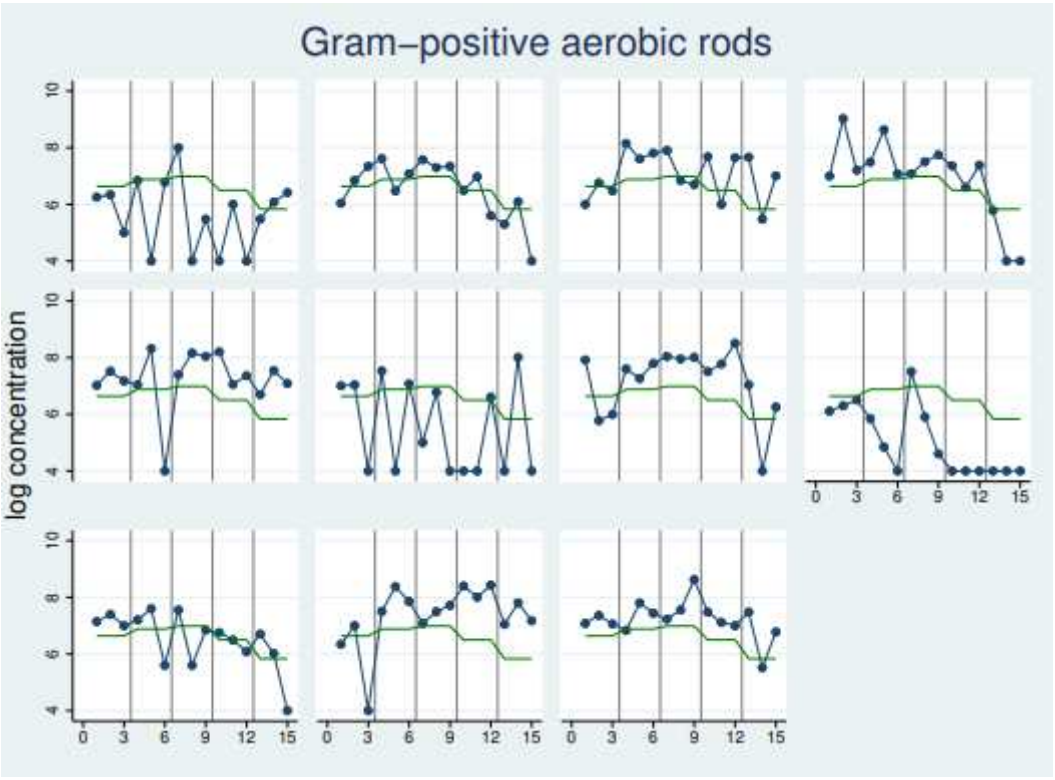

Figure 23

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Gram-positive aerobic rods for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

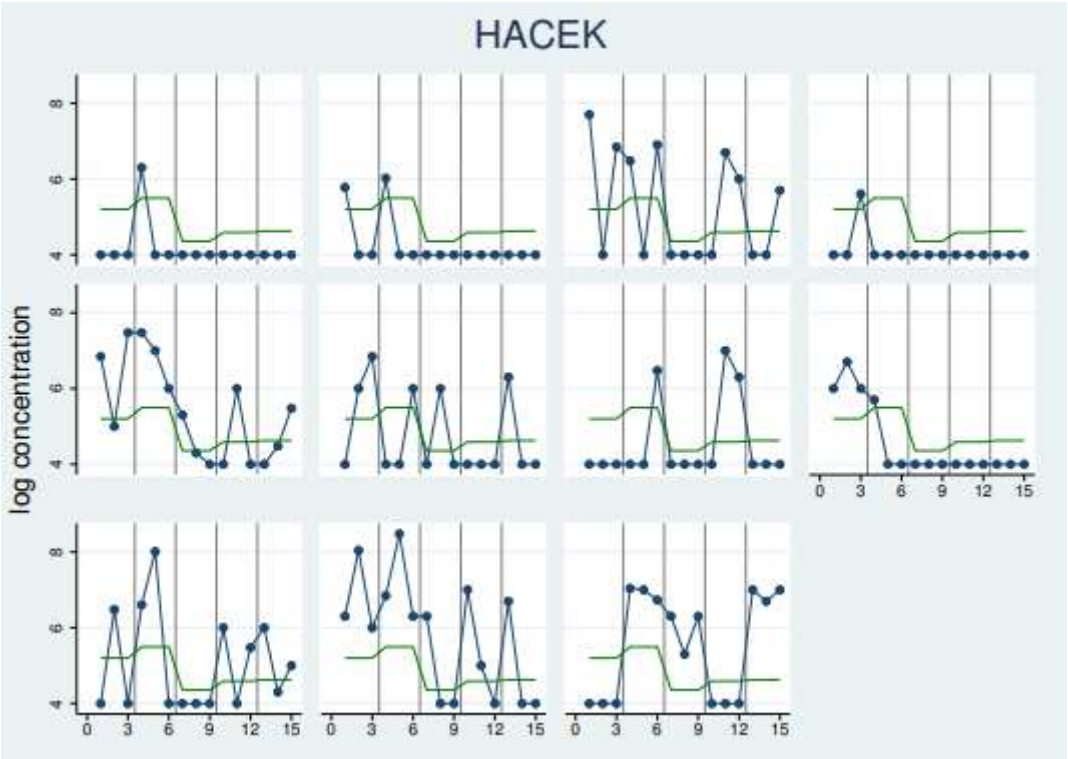

Figure 24

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Hacek for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

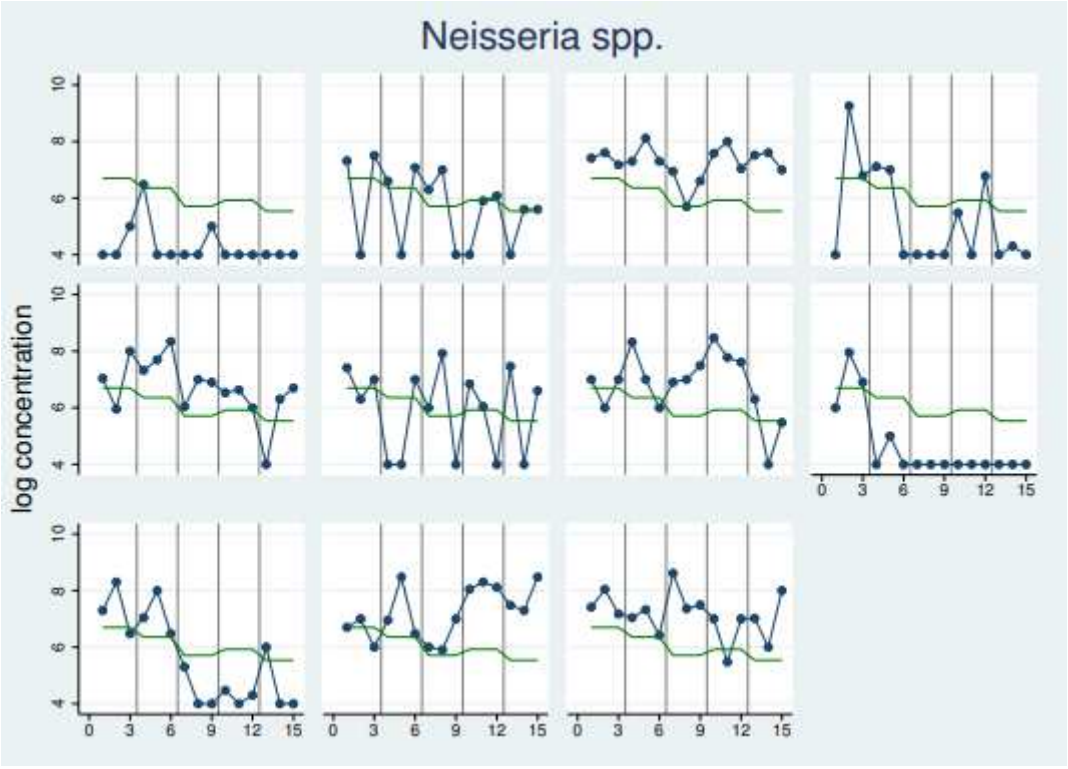

Figure 25

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Neisseria spp. for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

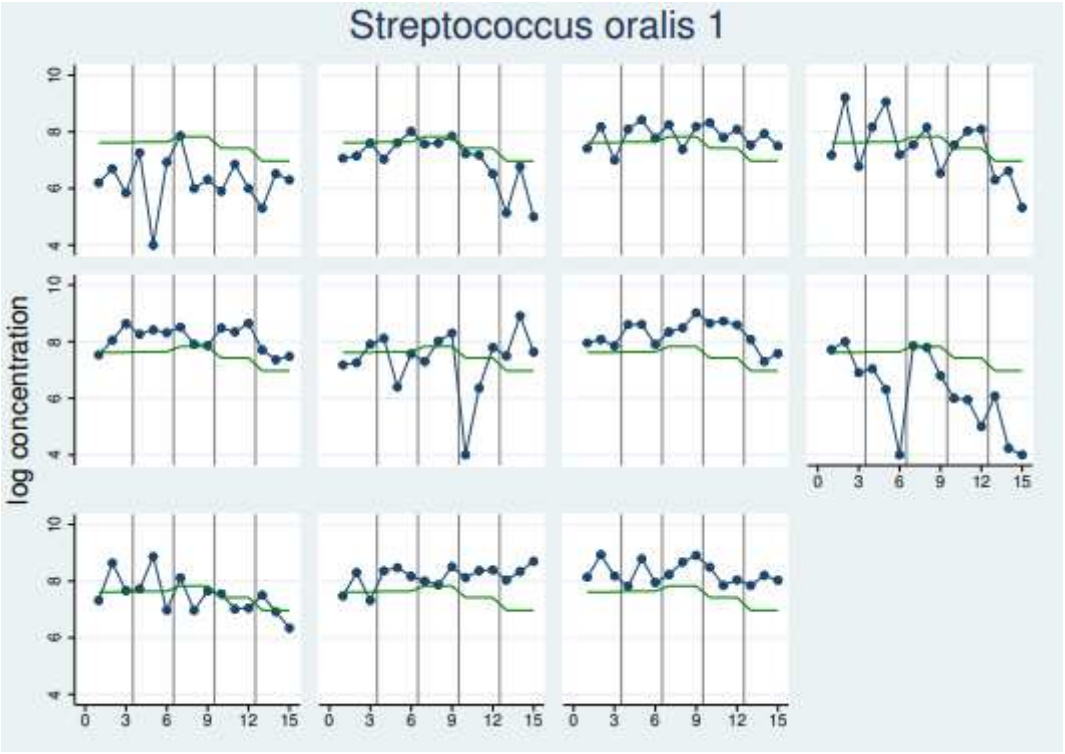

Figure 26

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Streptococcus oralis 1 for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

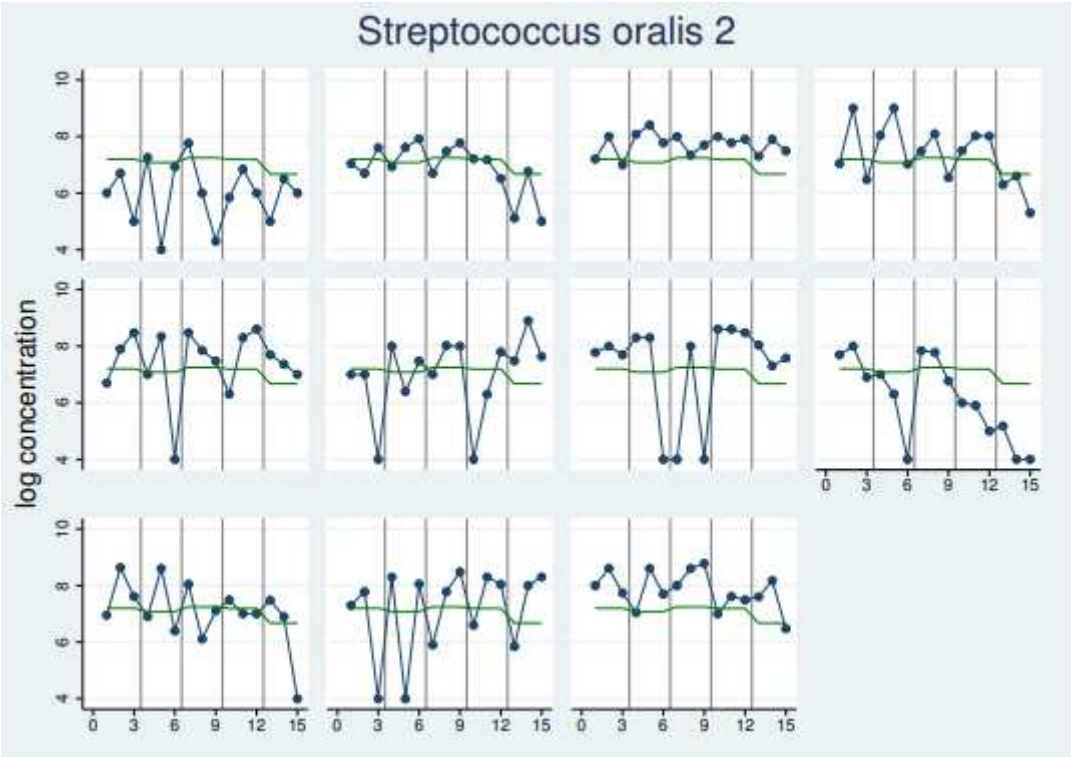

Figure 27

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Streptococcus oralis 2 for each of the 11 participants over the 5 phases. Green line: mean value per phase, grey line: end of the phase.

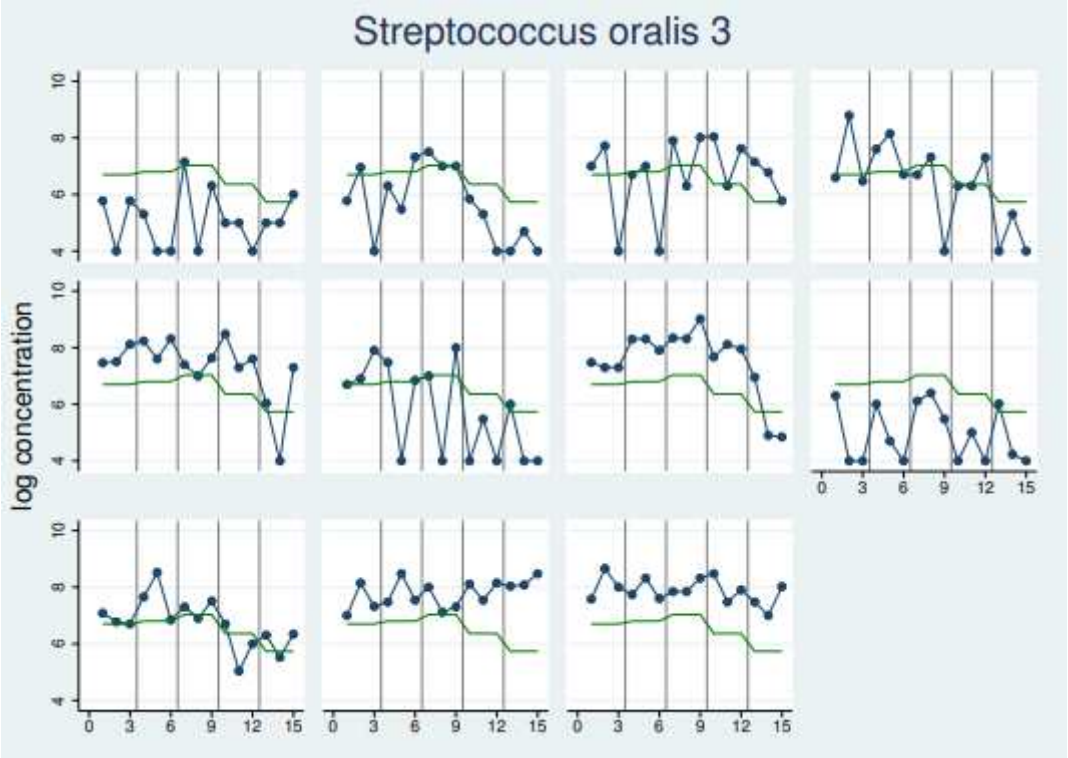

Figure 28

Scatter plot of individual bacterial concentration over time. Concentrations (in log-10 CFU per ml) of Streptococcus oralis 3 for each of the 11 participantsover the 5 phases. Green line: mean value per phase, grey line: end of the phase.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- additionalfile1.pdf