Supplementary material for
Modelling the effect of birth and feeding modes on the development of human gut microbiota

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1 Analysis of model using a quasi-steady state approximation

To obtain the simplified system using the quasi-steady-state approximation at $Z(t) = 0$, we apply the condition $B_1 = \hat{B}_1 = 0$. The original model at equilibria reduces to

$$\dot{B}_2 = rB_2(1 - B_2 - \alpha B_3) + f_2 = 0, \quad (S1)$$

$$\dot{B}_3 = rB_3(1 - B_3 - \alpha B_2) + f_3 = 0. \quad (S2)$$

We solve the quasi-steady-state approximation to obtain the equilibria of the system analytically. We add (S1) and (S2) to obtain

$$r\left(-B_2^2 - 2\alpha B_2 B_3 + B_2 - B_3^2 + B_3\right) + f_2 + f_3 = 0, \quad (S3)$$

and then subtract (S1) and (S2) to obtain

$$r\left(-B_2^2 + B_3^2 + B_2 - B_3\right) + f_2 - f_3 = 0. \quad (S4)$$

Thus, from (S4) we have

$$B_2 - B_2^2 = \frac{-(B_3 - 1)B_3 r - f_2 + f_3}{r}. \quad (S5)$$

Substituting (S5) into (S3), we obtain

$$2\left(f_3 - B_3 r(\alpha B_2 + B_3 - 1)\right) = 0, \quad (S6)$$

which simplifies to

$$B_2 = \frac{f_3 - (B_3 - 1)B_3 r}{\alpha B_3 r}. \quad (S7)$$

We then substitute (S7) into (S4) to obtain a quartic function of B_3

$$aB_3^4 + bB_3^3 + cB_3^2 + dB_3 + e = 0, \tag{S8}$$

where

$$\begin{aligned}
a &= \left(\alpha^2 - 1\right) r^2, \\
b &= (\alpha - 1)(\alpha + 2)\left(-r^2\right), \\
c &= r\left(\alpha^2 f_2 - \left(\alpha^2 - 2\right) f_3 + (\alpha - 1)r\right), \\
d &= (\alpha - 2) f_3 r, \\
e &= -f_3^2.
\end{aligned}$$

From (S1), we can solve for the nullclines

$$B_2 = \frac{r - \alpha B_3 r \pm \sqrt{(r - \alpha B_3 r)^2 + 4 f_2 r}}{2r}.$$

Since $4f_2 r > 0$,

$$\sqrt{(r - \alpha B_3 r)^2 + 4 f_2 r} > \mid r - \alpha B_3 r \mid,$$

and thus

$$B_2 = \frac{r - \alpha B_3 r + \sqrt{(r - \alpha B_3 r)^2 + 4 f_2 r}}{2r} > 0, \tag{S9}$$

$$B_2 = \frac{r - \alpha B_3 r - \sqrt{(r - \alpha B_3 r)^2 + 4 f_2 r}}{2r} < 0. \tag{S10}$$

Similarly, from (S2), the nullclines for B_3 are

$$B_3 = \frac{r - \alpha B_2 r \pm \sqrt{(r - \alpha B_2 r)^2 + 4 f_3 r}}{2r},$$

where

$$B_3 = \frac{r - \alpha B_2 r + \sqrt{(r - \alpha B_2 r)^2 + 4 f_3 r}}{2r} > 0, \tag{S11}$$

$$B_3 = \frac{r - \alpha B_2 r - \sqrt{(r - \alpha B_2 r)^2 + 4 f_3 r}}{2r} < 0. \tag{S12}$$

The bacterial populations B_2 and B_3 are always positive. Therefore, we only consider the nullclines (S9) and (S11)

Substituting the expression for B_3 (S11) into B_2 (S9), we get

$$\frac{1}{2}\alpha\left(\sqrt{(r-\alpha B_2 r)^2+4f_3 r}+\alpha(-B_2)r+r\right)+2B_2 r-r=$$
$$\sqrt{\left(r-\frac{1}{2}\alpha\left(\sqrt{(r-\alpha B_2 r)^2+4f_3 r}+\alpha(-B_2)r+r\right)\right)^2+4f_2 r}\,.$$

We replace B_2 with B for notational simplicity. Squaring the LHS and RHS we get

$$LHS^2=\frac{1}{2}\alpha^4B^2r^2-2\alpha^2B^2r^2+4B^2r^2+$$
$$\left(-\frac{1}{2}\alpha^3Br+2\alpha Br+\frac{\alpha^2 r}{2}-\alpha r\right)\sqrt{(r-\alpha Br)^2+4f_3 r}-$$
$$\alpha^3Br^2+\alpha^2Br^2+2\alpha Br^2-4Br^2+\alpha^2 f_3 r+\frac{\alpha^2r^2}{2}-\alpha r^2+r^2,$$

and

$$RHS^2=\frac{1}{2}\alpha^4B^2r^2-\alpha^3Br^2+\alpha^2Br^2+\alpha^2 f_3 r+4f_2 r+\frac{\alpha^2r^2}{2}-\alpha r^2+r^2$$
$$\left(-\frac{1}{2}\alpha^3Br+\frac{\alpha^2 r}{2}-\alpha r\right)\sqrt{(r-\alpha Br)^2+4f_3 r}.$$

Let $LHS^2=RHS^2$:

$$r\left(-\alpha B\sqrt{r\left(r(\alpha B-1)^2+4f_3\right)}+Br\left(-\alpha+\left(\alpha^2-2\right)B+2\right)+2f_2\right)=0.$$

Because $r\neq 0$, we get

$$-\alpha B\sqrt{r\left(r(\alpha B-1)^2+4f_3\right)}+Br\left(-\alpha+\left(\alpha^2-2\right)B+2\right)+2f_2=0$$
$$\Rightarrow Br\left(-\alpha+\left(\alpha^2-2\right)B+2\right)+2f_2=\alpha B\sqrt{r\left(r(\alpha B-1)^2+4f_3\right)}.$$

Again taking the square both sides and simplifying, we obtain

$$\left(\alpha^2-1\right)B^4r^2-\left(\alpha^2+\alpha-2\right)B^3r^2+$$
$$B^2r\left(\alpha^2 f_3-\left(\alpha^2-2\right)f_2+(\alpha-1)r\right)+(\alpha-2)Bf_2r-f_2^2=0. \tag{S13}$$

The coefficients of the quartic equation from high to low degree are:

$$[\overbrace{\left(\alpha^2-1\right)r^2}^{4},\quad \overbrace{\left(\alpha^2+\alpha-2\right)\left(-r^2\right)}^{3},$$
$$\overbrace{r\left(\alpha^2 f_3-\left(\alpha^2-2\right)f_2+(\alpha-1)r\right)}^{2},\quad \overbrace{(\alpha-2)f_2 r}^{1},\quad \overbrace{-f_2^2}^{0}]$$

Provided $\alpha > 0, r > 0, f_2 > 0, f_3 > 0, f_2 \ll r$ and $f_3 \ll r$ as per our definitions of the parameters, we get the following conditions for positive coefficients:

$$\left(\alpha^2-1\right)r^2 > 0 \Rightarrow \alpha > 1,$$
$$\left(\alpha^2+\alpha-2\right)\left(-r^2\right) > 0 \Rightarrow 0 < \alpha < 1,$$

$$\begin{aligned}
&r\left(\alpha^2 f_3-\left(\alpha^2-2\right)f_2+(\alpha-1)r\right) > 0,\\
&\Rightarrow \begin{cases} \frac{r-\sqrt{r^2-4(f_2-f_3)(r-2f_2)}}{2(f_2-f_3)} < \alpha < \frac{r+\sqrt{r^2-4(f_2-f_3)(r-2f_2)}}{2(f_2-f_3)} & \text{if } 0 < f_3 < f_2 \\ \alpha > 1-\frac{2f_2}{r} & \text{if } f_2 = f_3, \\ \alpha > \frac{r-\sqrt{r^2-4(f_2-f_3)(r-2f_2)}}{2(f_2-f_3)} & \text{if } f_3 > f_2, \end{cases}\\
&\simeq \begin{cases} \frac{r-\sqrt{(r-2(f_2-f_3))^2}}{2(f_2-f_3)} \simeq 1 < \alpha < \frac{r+\sqrt{r^2-4r(f_2-f_3)}}{2(f_2-f_3)} & \text{if } 0 < f_3 < f_2, \\ \alpha > 1 & \text{if } f_2 = f_3, \\ \alpha > \frac{r-\sqrt{(r-2(f_2-f_3))^2}}{2(f_2-f_3)} \simeq 1 & \text{if } f_3 > f_2, \end{cases}
\end{aligned}$$

$$(\alpha-2)f_2 r > 0 \Rightarrow \alpha > 2,$$

$$-f_2^2 < 0.$$

We then use the Descartes' rule of signs to determine the number of positive real roots, therefore the number of positive equilibira, of the quasi-steady-state. This is summarised in Table S1.

Table S1: Sign analysis for quartic coefficients

α	Sign of the coefficients	Number of positive real roots
$0 < \alpha < 1$	$[- + - - -]$	2 or 0
$\alpha = 1$	$[+ - -]$	1
$1 < \alpha < 2$	$[+ - + - -]$	3 or 1
$\alpha = 2$	$[+ - + -]$	3 or 1
$\alpha > 2$	$[+ - + + -]$	3 or 1

2 Supplementary figures

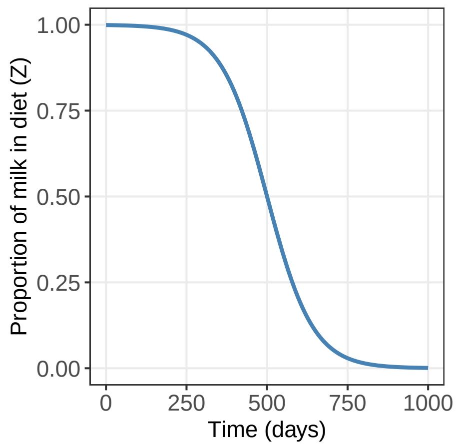

Figure S1: The proportion of milk in infant's diet over time given by function $Z(t) = \frac{1}{1+e^{\omega(t-h)}}$, where h controls the horizontal positioning (timing of weaning) and ω controls the slope (speed of weaning).

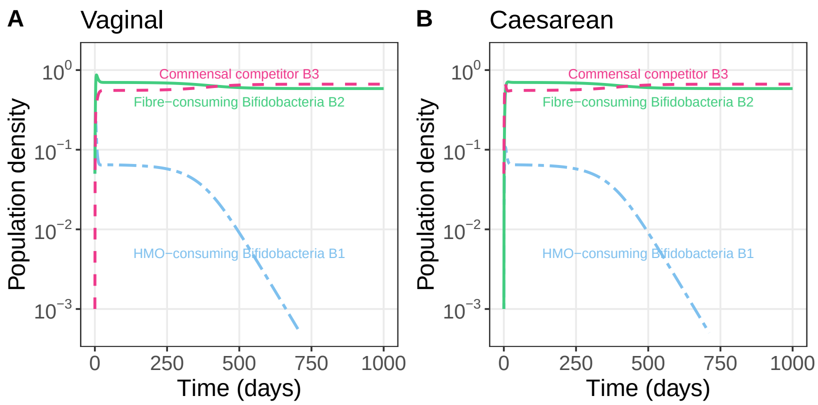

Figure S2: Longitudinal dynamics of the three bacterial populations with low between-population competition ($\alpha = 0.7$) and initial conditions representing vaginal birth (A) and C-section (B); other parameters are set at baseline values (given in Table 1 in the main text). The blue two-dash line represents the infant-type Bifidobacteria $B1$, the green solid line represents the adult-type Bifidobacteria $B2$, and the red dashed line represents the commensal competitor $B3$. The y-axes population densities on a log scale. The dynamics are simulated for three years allowing the system to reach a post-weaning steady state. Birth modes have no effect on the long-term microbial profile here because the system only has one equilibrium as described in section 3.1 and shown in Figure 3A in the main text.

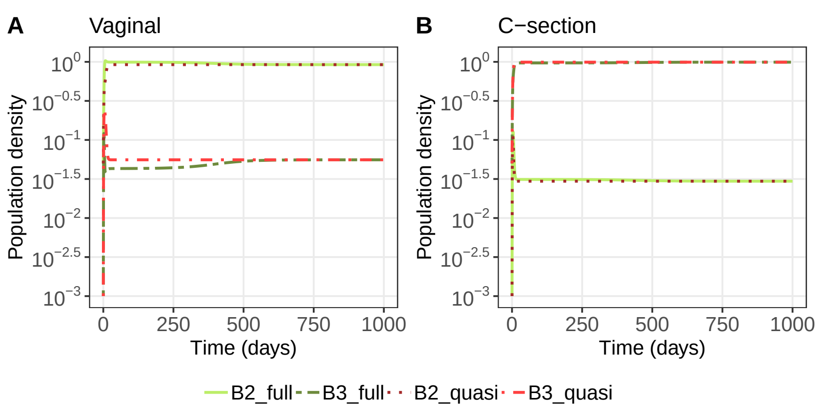

Figure S3: Dynamics of the original model (green) and its quasi-steady-state approximation (red) over time using baseline parameters. Light green lines represent fibre-consuming Bifidobacteria $B2$, and dark green line represent Commensal competitor $B3$ in the original model. Dotted red lines represent $B2$, and dot-dash red lines represent $B3$ at quasi-steady-state approximation. Parameters are set at baseline values (given in Table 1 in the main text).

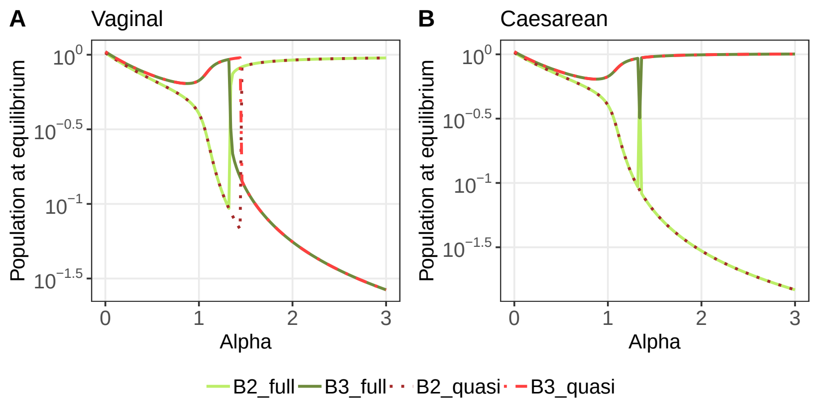

Figure S4: The long-term equilibria of the original model (green) versus that of the quasi-steady-state approximation (red) against a range of α values. Light green lines represent fibre-consuming Bifidobacteria $B2$, and dark green line represent Commensal competitor $B3$ in the original model. Dotted red lines represent $B2$, and dot-dash red lines represent $B3$ at quasi-steady-state approximation. Other parameters are set at baseline values (Table 1).

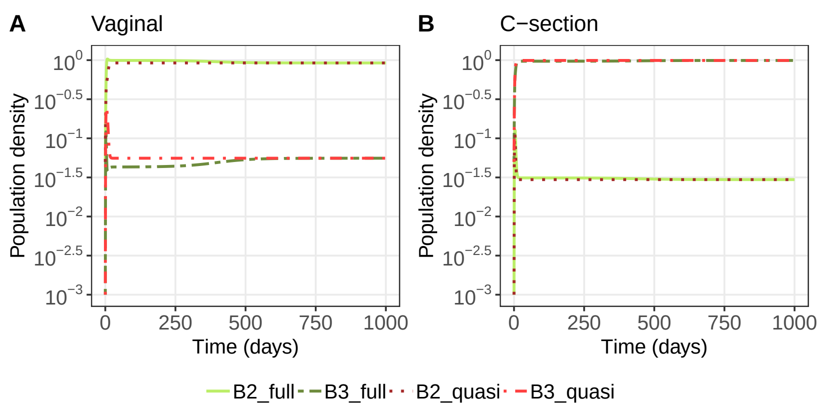

Figure S5: The long-term equilibria of the original model (green) versus that of the quasi-steady-state approximation (red) against a range of h values (half-life of milk). Light green lines represent fibre-consuming Bifidobacteria $B2$, and dark green line represent Commensal competitor $B3$ in the original model. Dotted red lines represent $B2$, and dot-dash red lines represent $B3$ at equilibrium given the quasi-steady-state approximation. Other parameters are set at baseline values (Table 1).

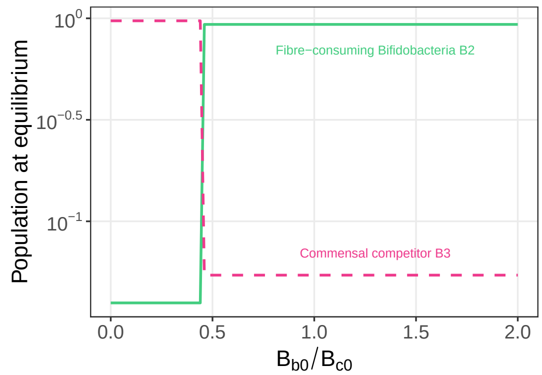

Figure S6: Changing the initial colonisation make the system switch from one equilibrium to another. The initial conditions are expressed as a ratio of Bifidobacteria on commensal competitor B_{b0}/B_{c0}, where B_{b0} is the initial value of Bifidobacteria $(B_1 + B_2)$, and B_{c0} is the initial value of the commensal competitor. Other parameters are as specified in Table 1.

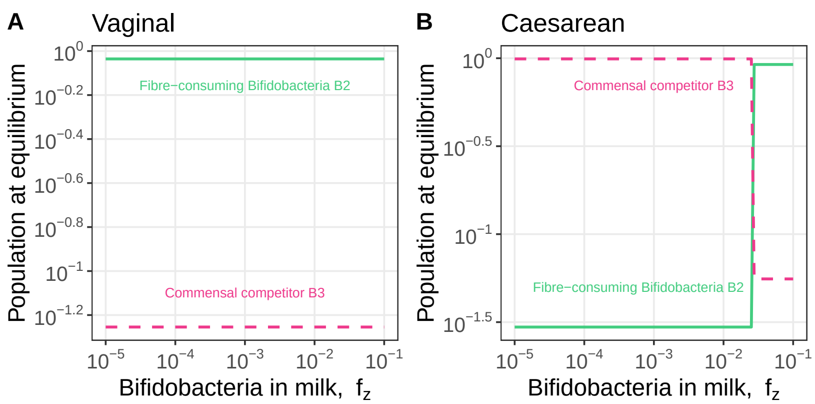

Figure S7: Long-term equilibria of $B2$ and $B3$ against a range of f_z values. Other parameters are set at baseline values (Table 1). The initial condition for C-section is used.

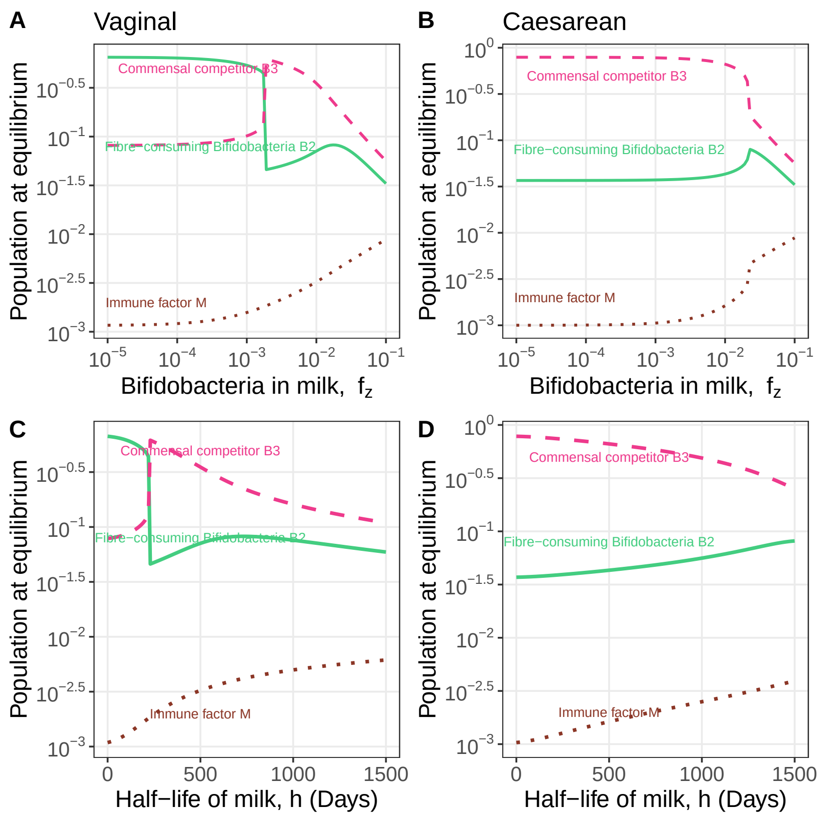

Figure S8: The effect of breast milk and weaning schedule in a version of the extended model where Bifidobacteria $B2$ are subject to the same strength of immune clearance as the commensals $B3$ ($\mu_b = \mu_c = 200$). Other parameters are set at baseline values (given in Table 1 in the main text). Initial conditions representing vaginal birth (A and C) and C-section (B and D) are used. The blue two-dash line represents the infant-type Bifidobacteria $B1$, the green solid line represents the adult-type Bifidobacteria $B2$, the red dashed line represents the commensal competitor $B3$, and the brown dotted line represents immune factor M. The y-axes are log-scaled population densities at equilibria. The x-axes of panels A and B are log-scaled Bifidobacteria levels carried by milk f_z representing the amount of breast milk in diet, and the time h when milk takes up 50% of the diet (C and D) representing the duration of breastfeeding. In comparison to Figure 4 in the main text, the Bifidobacteria $B2$ here is suppressed by a higher level of breast milk due to the immune effect and competition with $B3$.

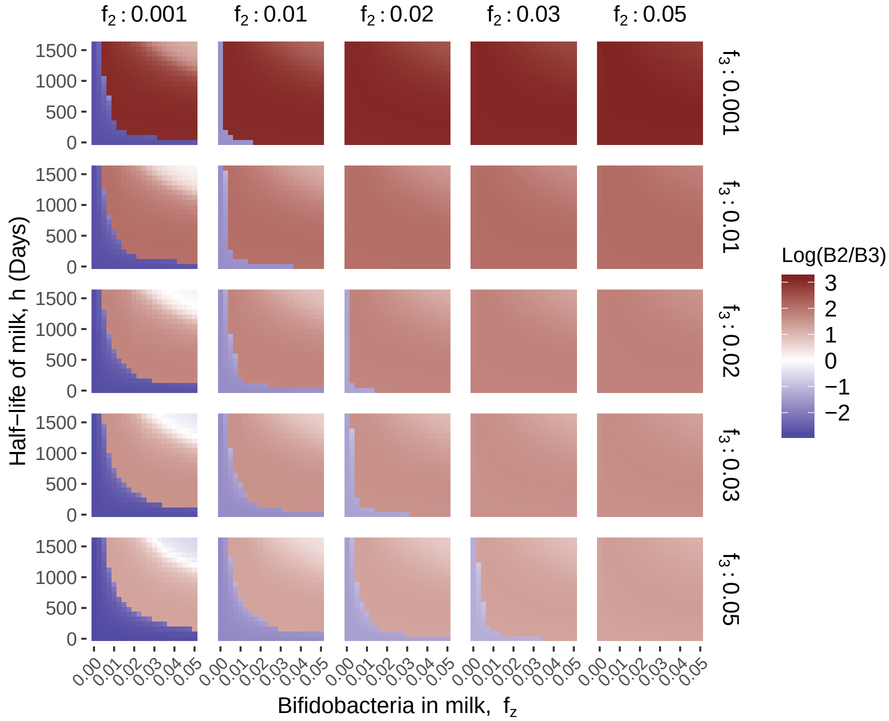

Figure S9: The effect of feeding practices (h and f_z) and bacteria supply from the environment (f_2 and f_3) on the relative abundance of Bifidobacteria against commensal. The ratio of fibre-consuming Bifidobacteria to commensal competitor at equilibria is shown in colour and expressed on a log scale (Ratio $= \log_{10}(B_2/B_3)$). Blue indicates a negative $\log_{10}(B_2/B_3)$ value, which means the abundance of Bifidobacteria is lower than commensal ($B_2/B_3 < 1$). Each panel shows this ratio against a range of h (the half life of milk) and f_z (the amount of breast milk) values. Panels from left to right have increasing f_2 values (supply of Bifidobacteria $B2$ from the environment). Panels from top to bottom have increasing f_3 values (supply of commensal from the environment).

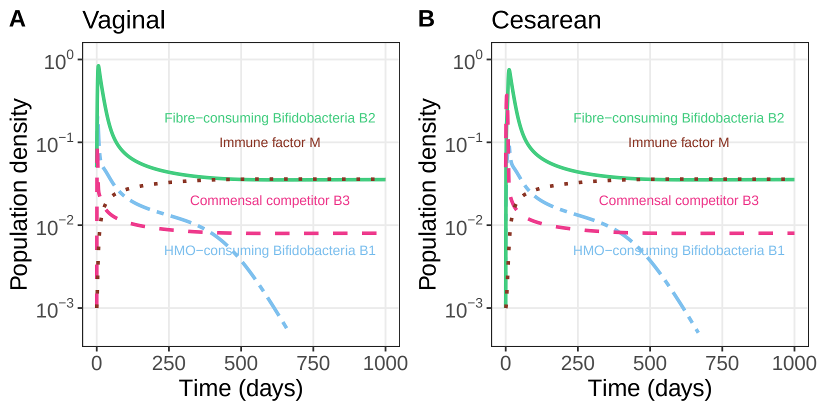

Figure S10: Longitudinal dynamics of a generalised model with immune response where $\dot{M} = \gamma(B_1 + B_2) - \mu M$. We define γ and μ as the rates of growth and decay of the immune response. We use $\mu = \gamma = 0.001$, other parameters are set at baseline values (given in Table 1 in the main text). The blue two-dash line represents the infant-type Bifidobacteria $B1$, the green solid line represents the adult-type Bifidobacteria $B2$, and the red dashed line represents the commensal competitor $B3$. The dynamics are simulated for three years allowing the system to reach a post-weaning steady state. In this version, the long-term microbial configuration is insensitive to birth modes because the stable state is dominated by the effect of immune clearance.

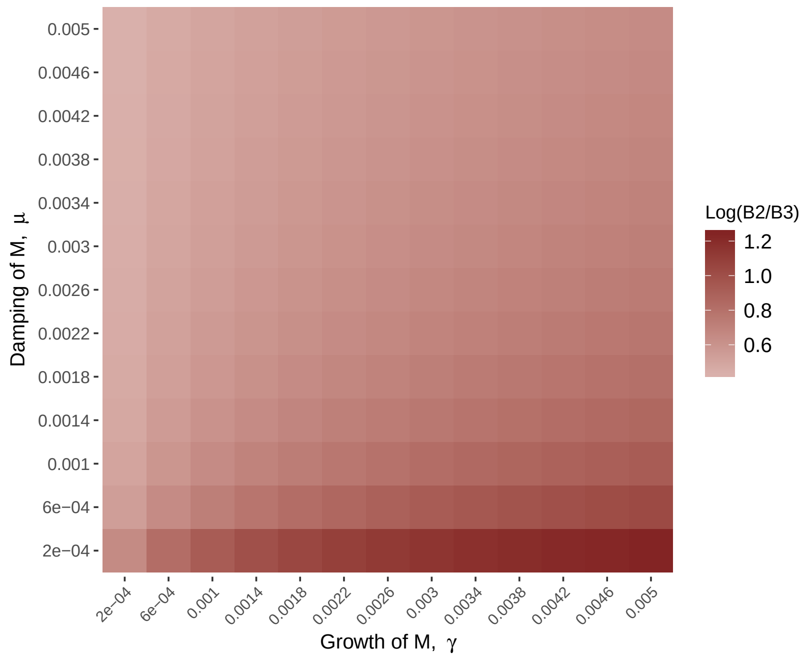

Figure S11: The effect of γ and μ in the generalised model with immune response where $\dot{M} = \gamma(B_1 + B_2) - \mu M$. We define γ and μ as the rates of growth and decay of the immune response. We use $\mu = \gamma = 0.001$, other parameters are set at baseline values (given in Table 1 in the main text). The relative abundance of Bifidobacteria against commensals is given for different combinations of γ and μ. The ratio of fibre-consuming Bifidobacteria to commensal competitor at equilibria is shown in colour and expressed on a log scale (Ratio $= \log_{10}(B_2/B_3)$). Red indicates a positive $\log_{10}(B_2/B_3)$ value, which means the abundance of Bifidobacteria is higher than commensal ($B_2/B_3 > 1$). The growth of the immune response γ promotes the establishment of Bifidobacteria $B2$ while the decay in the immune response, μ, dampens the establishment of $B2$.