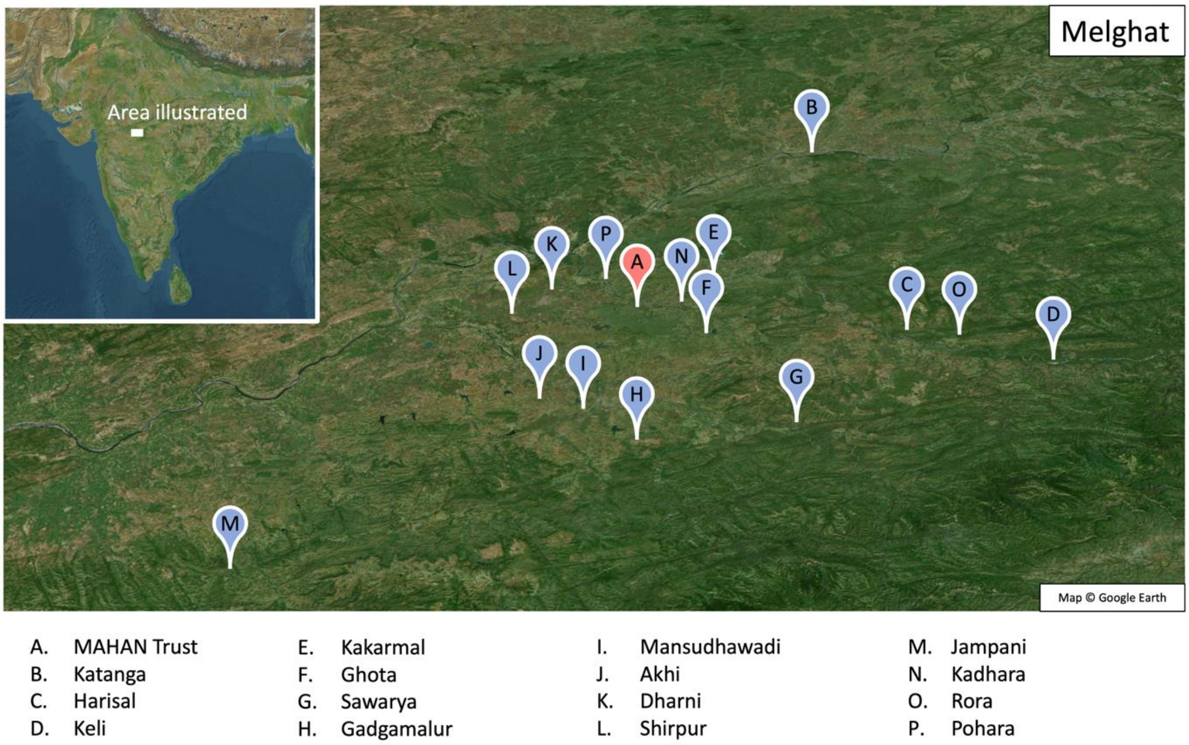
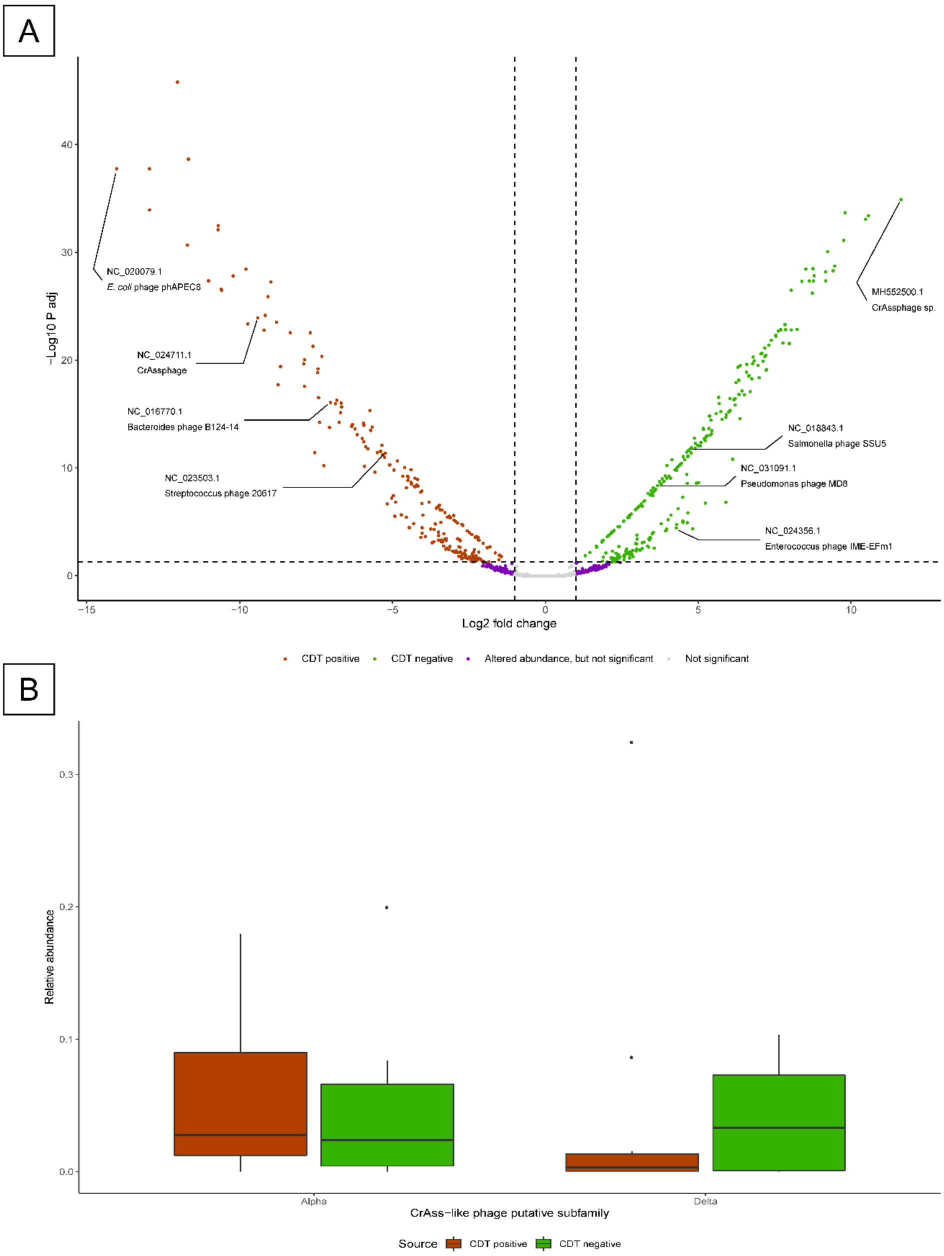
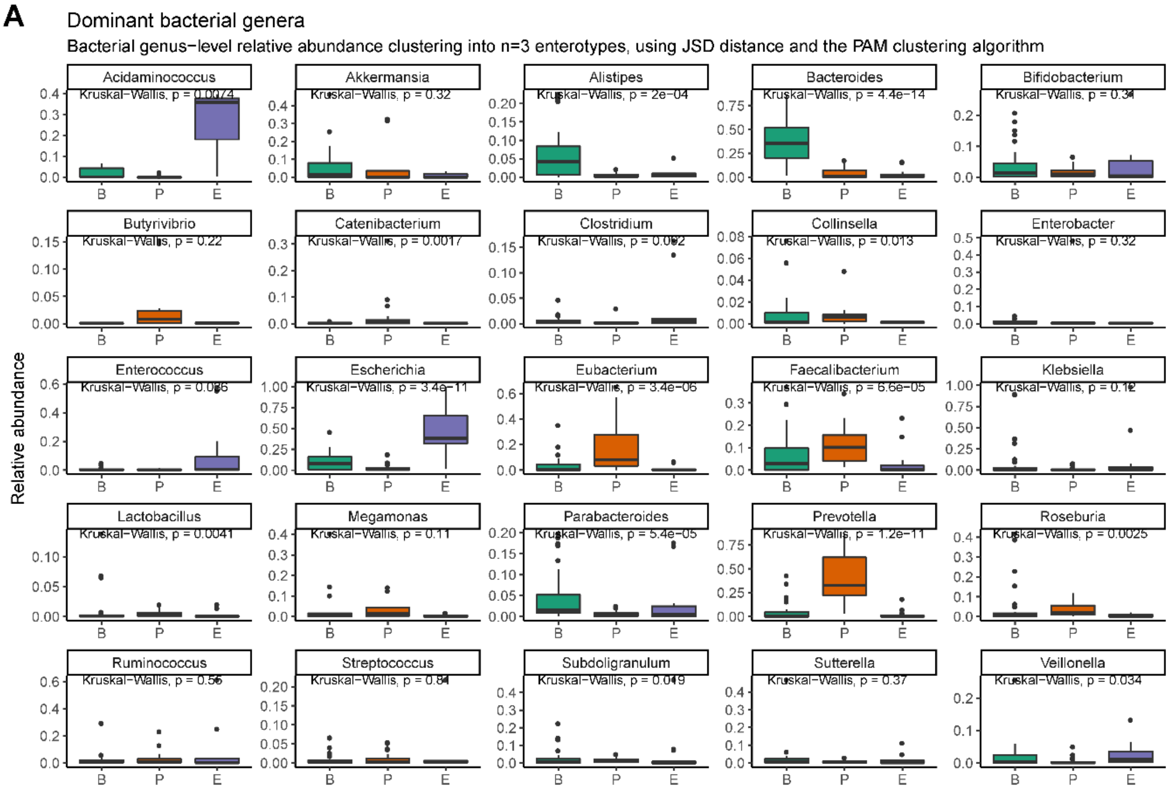


SUPPLEMENTARY FIGURE 1. Mapped locations of Melghat villages participating in the study

SUPPLEMENTARY FIGURE 2. Traditional Melghat tribal village

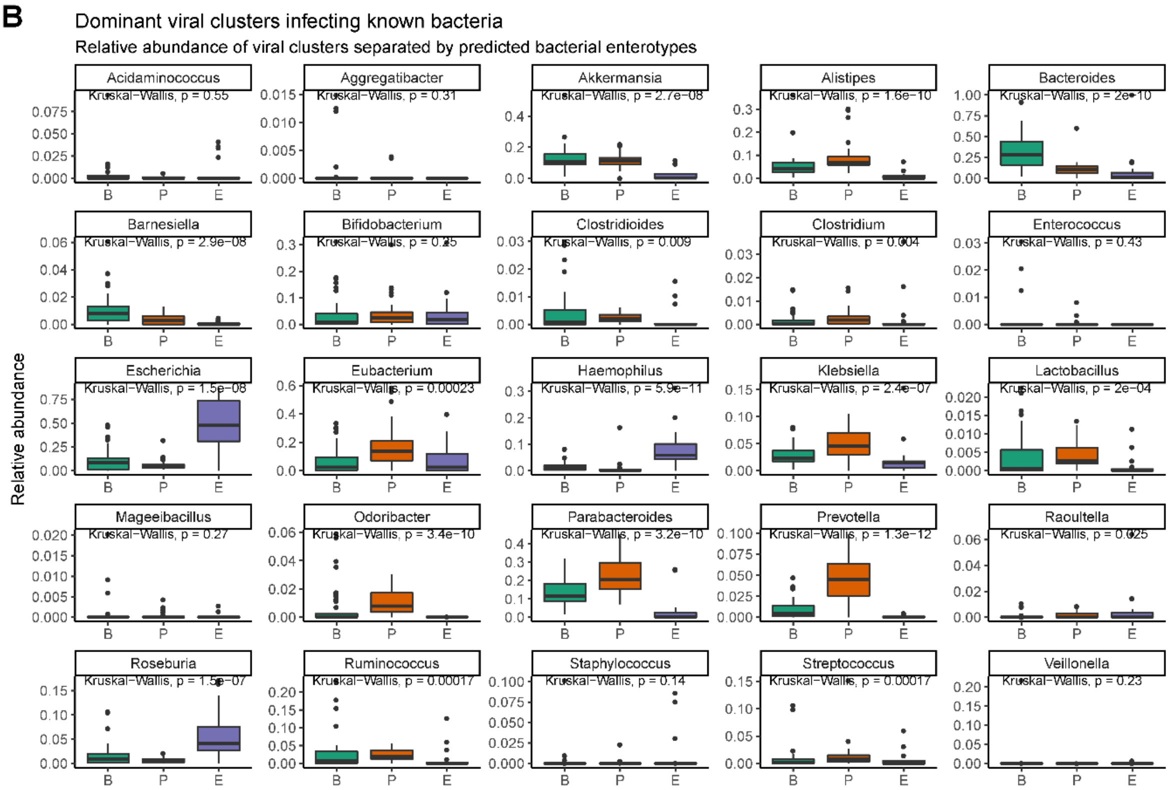


SUPPLEMENTARY FIGURE 3. Volcano plot of the fold change versus statistical significance of Viral Clusters (VCs). The top BLAST hit, and accession number, for several VCs are highlighted. **(B)** Examination of the relative abundance of putative crAss-like phage subfamilies alpha and delta, predicted to infect *Bacteroides* and *Prevotella*, respectively. No statistical differences were observed between crAss-like phage abundances by CDT status or geographical residence (Kruskal-Wallis test; CDT status: p-values 0.6 and 0.47, respectively; Geography: p-values 0.76 and 0.059, respectively).



Dominant bacterial genera

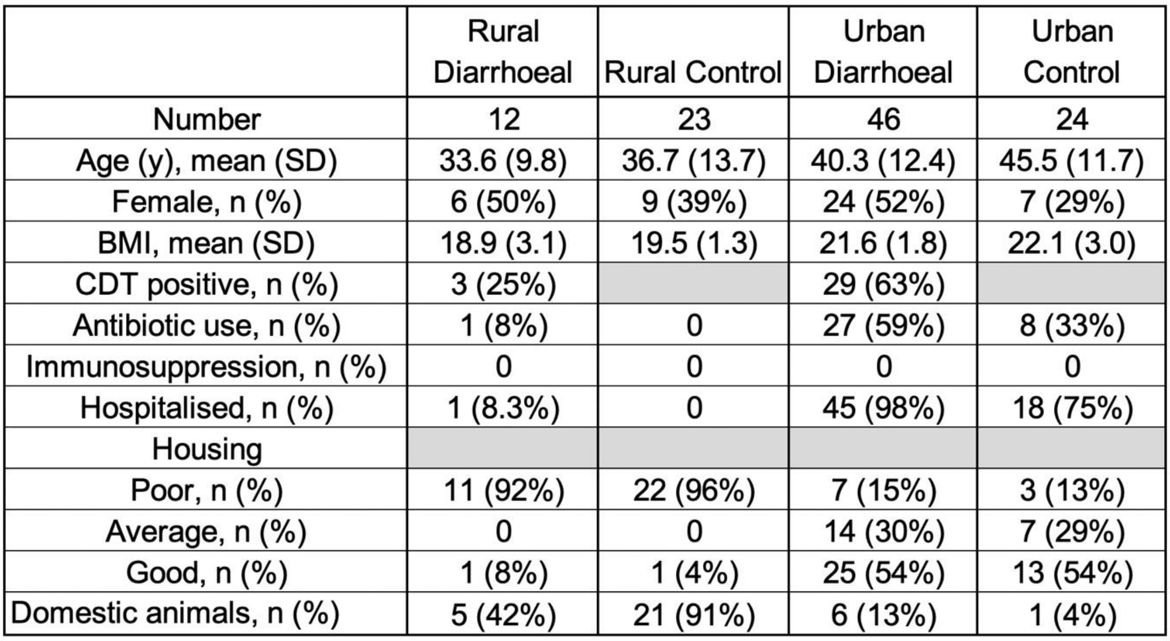
Bacterial genus−level relative abundance clustering into n=3 enterotypes, using JSD distance and the PAM clustering algorithm



Dominant viral clusters infecting known bacteria

Relative abundance of viral clusters separated by predicted bacterial enterotypes

SUPPLEMENTARY FIGURE 4. Relative abundance of the top 25 most dominant (A) bacteria, and (B) viral clusters. Bacterial enterotypes (n=3) were dominated by *Bacteroides* (B), *Prevotella* (P), and *Escherichia* (E). Abundant viruses in faecal samples conforming to the B, P, and E enterotypes similarly infect *Bacteroides*, *Prevotella*, and *Escherichia*, respectively. However, for some lower abundant bacterial taxa (e.g. *Parabacteroides*), a corresponding abundance of its infecting viruses by enterotype was not observed.



	Rural Diarrhoeal	Rural Control	Urban Diarrhoeal	Urban Control
Number	12	23	46	24
Age (y), mean (SD)	33.6 (9.8)	36.7 (13.7)	40.3 (12.4)	45.5 (11.7)
Female, n (%)	6 (50%)	9 (39%)	24 (52%)	7 (29%)
BMI, mean (SD)	18.9 (3.1)	19.5 (1.3)	21.6 (1.8)	22.1 (3.0)
CDT positive, n (%)	3 (25%)		29 (63%)	
Antibiotic use, n (%)	1 (8%)	0	27 (59%)	8 (33%)
Immunosuppression, n (%)	0	0	0	0
Hospitalised, n (%)	1 (8.3%)	0	45 (98%)	18 (75%)
Housing				
Poor, n (%)	11 (92%)	22 (96%)	7 (15%)	3 (13%)
Average, n (%)	0	0	14 (30%)	7 (29%)
Good, n (%)	1 (8%)	1 (4%)	25 (54%)	13 (54%)
Domestic animals, n (%)	5 (42%)	21 (91%)	6 (13%)	1 (4%)

SUPPLEMENTARY TABLE 1. Baseline Cohort Characteristics for Metagenome Cohort

Taxa	**Fold Change Urban vs Rural**	**FDR p.corr**
Roseburia intestinalis	0.02	1.9×10^{-7}
Bacteroides intestinalis	29.26	1.7×10^{-5}
Megamonas funiformis	28.58	0.0001
Roseburia hominis	0.07	0.0007
Ruminococcus bromii	0.06	0.0014
Parabacteroides unclassified	11.50	0.0034
Lactobacillus ruminis	0.28	0.0083
Parabacteroides distasonis	9.23	0.0084
Catenibacterium mitsuokai	0.11	0.0125
Bacteroides thetaiotaomicron	8.42	0.0125
Veillonella parvula	8.94	0.0186
Enterobacter cloacae	8.28	0.0192
Subdoligranulum unclassified	3.98	0.0192
Prevotella stercorea	0.38	0.0225
Acidaminococcus intestini	0.12	0.0225
Megamonas hypermegale	9.28	0.0242
Haemophilus parainfluenzae	0.13	0.0252
Alistipes unclassified	0.15	0.0252
Escherichia unclassified	5.43	0.0342
Veillonella dispar	6.15	0.0422
Bacteroides vulgatus	2.49	0.0422
Alistipes finegoldii	6.01	0.0422
Paraprevotella clara	6.04	0.0422
Megamonas unclassified	7.32	0.0422
Bacteroides uniformis	5.31	0.0422
Enterococcus faecium	7.45	0.0422

SUPPLEMENTARY TABLE 2. Bacterial taxa enriched in Urban vs Rural subjects

Taxa	**Fold Change Diarrhoeal vs Non-diarrhoeal**	**FDR p.corr**
Eubacterium siraeum	0.04	1.81×10^{-8}
Mitsuokella multacida	0.05	1.44×10^{-7}
Barnesiella intestinihominis	0.09	0.0002
Collinsella aerofaciens	0.54	0.0017
Bacteroides ovatus	5.35	0.0050
Prevotella copri	0.35	0.0050
Bacteroides dorei	6.45	0.0069
Bacteroides uniformis	4.39	0.0132
Enterococcus faecium	5.48	0.0132
Ruminococcus bromii	0.20	0.0132
Bifidobacterium angulatum	0.23	0.0205
Bacteroidales bacterium ph8	0.22	0.0223
Subdoligranulum unclassified	0.40	0.0246
Clostridium nexile	4.64	0.0275
Roseburia intestinalis	4.16	0.0417
Bacteroides xylanisolvens	3.62	0.0448

SUPPLEMENTARY TABLE 3. Bacterial taxa enriched in Diarrhoeal vs Non-diarrhoeal subjects

Taxa	**Fold Change** **CDT Positive vs Negative**	**FDR p.corr**
Coprobacillus unclassified	35.23	$1.72\text{x}10^{-7}$
Bacteroides ovatus	17.28	$6.08\text{x}10^{-6}$
Lachnospiraceae bacterium 2-1-58FAA	22.90	$1.42\text{x}10^{-5}$
Megamonas unclassified	0.05	0.0006
Catenibacterium mitsuokai	0.07	0.0009
Bacteroides fragilis	3.59	0.0017
Eubacterium eligens	0.09	0.0019
Enterococcus faecium	0.10	0.0046
Eubacterium rectale	0.32	0.0046
Barnesiella intestinihominis	0.11	0.0049
Bifidobacterium adolescentis	0.10	0.0060
Bifidobacterium breve	8.40	0.0113
Ruminococcus gnavus	7.71	0.0141
Alistipes indistinctus	8.35	0.0149
Bacteroides eggerthii	7.58	0.0190
Parabacteroides distasonis	5.85	0.0296
Dialister succinatiphilus	0.14	0.0335
Bacteroides intestinalis	5.95	0.0493

SUPPLEMENTARY TABLE 4. Bacterial taxa enriched in *C. difficile* toxin (CDT) positive subjects

Gene cluster	**Rural**		**Urban**		**P value (Chi-squared)**
	Proportion (n=35)	**Percentage %**	**Proportion (n=70)**	**Percentage %**	
Ambler Class A					
CTX	11/35	31.4	58/70	82.9	5.3×10^{-7}
KPC	0/35	0	0/70	0	-
TEM	10/35	28.6	53/70	75.7	9.1×10^{-6}
SHV	2/35	5.7	25/70	35.7	0.002
Ambler Class B					
IMP	0/35	0	0/70	0	-
NDM	1/35	2.9	32/70	45.7	2.3×10^{-5}
VIM	0/35	0	0/70	0	-
Ambler Class C					
BLAEC/AmpC	19/35	54.3	53/70	75.7	0.045
Ambler Class D					
OXA	4/35	11.4	48/70	68.6	1.1×10^{-7}

SUPPLEMENTARY TABLE 5. Proportions of subjects with carriage detected of key beta-lactamase gene clusters

Pathway	**Rural Associated Taxa**				**Urban Associated Taxa**				**Total Rural**	**Total Urban**
	Ps	**Pc**	**Er**	**Rb**	**Ec**	**Kp**	**Bv**	**Pd**		
alpha-Linolenic acid metabolism	0	0	1	0	5	6	0	1	1	12
Benzoate degradation	1	2	5	3	6	33	3	4	11	46
Drug metabolism - cytochrome P450	0	0	1	0	8	11	1	1	1	21
Fluorobenzoate degradation	0	0	0	0	2	8	0	0	0	10
Furfural degradation	0	0	0	0	0	0	0	0	0	0
Lipoic acid metabolism	2	0	0	0	3	3	2	3	2	11
Penicillin and cephalosporin biosynthesis	0	0	0	0	0	0	2	0	0	2
Steroid degradation	0	0	0	0	1	1	0	0	0	2
Styrene degradation	0	0	0	0	0	3	0	0	0	3
Xylene degradation	0	0	2	1	0	9	1	0	3	10

SUPPLEMENTARY TABLE 6. Total kegg orthology (KO) gene copy numbers per pathway enriched in urban subjects for representative taxa from each group.

Ps = *Prevotella stercorea*, Pc = *Prevotella copri,* Er = *Eubacterium rectale*, Rb = *Ruminococcus bromii,* Ec = *Escherichia coli,* Kp = *Klebsiella pneumoniae*, Bv = *Bacteroides vulgatus,* Pd = *Parabacteroides distasonis*.

Pathway	Rural Associated Taxa				Urban Associated Taxa				Total Rural	Total Urban
	Ps	**Pc**	**Er**	**Rb**	**Ec**	**Kp**	**Bv**	**Pd**		
Alanine, aspartate and glutamate metabolism	19	29	23	19	27	41	29	36	90	133
Arginine and proline metabolism	11	22	24	13	41	67	24	35	70	167
Histidine metabolism	5	9	11	12	10	16	13	15	37	54
Peptidoglycan biosynthesis	18	18	17	17	23	26	15	20	70	84
Polyketide sugar unit biosynthesis	5	4	4	2	5	10	4	4	15	23
Starch and sucrose metabolism	18	34	36	20	36	49	31	49	108	165
Streptomycin biosynthesis	7	7	6	4	20	18	10	13	24	61
Terpenoid backbone biosynthesis	14	15	13	10	16	17	13	17	52	63
Thiamine metabolism	10	12	14	10	13	16	10	8	46	47
Valine, leucine and isoleucine biosynthesis	1	11	13	11	17	20	9	15	36	61

SUPPLEMENTARY TABLE 7. Total kegg orthology (KO) gene copy numbers per pathway enriched in rural subjects for representative taxa from each group.

Ps = *Prevotella stercorea*, Pc = *Prevotella copri,* Er = *Eubacterium rectale*, Rb = *Ruminococcus bromii*, Ec = *Escherichia coli,* Kp = *Klebsiella pneumoniae*, Bv = *Bacteroides vulgatus*, Pd = *Parabacteroides distasoni*

SUPPLEMENTARY MATERIALS

Dietary Information for Sampled Cohorts

As donor participants provided samples to CIIMS from geographically dispersed sites across Nagpur and Melghat, it was not possible to systematically administer customised and standardised food frequency questionnaires to each participant. However, it was possible to elicit the major constituents of the inpatient diets based on knowledge of the principal foods provided within the hospital sector. A typical oral dietary hospital regime consisted of a morning beverage (tea, coconut water, fruit juice or lemonade), a lunchtime choice of oatmeal, rice porridge (semi-solid preparation of rice and cumin seed with coriander or basil leaves), semolina, curd rice or dal khichdi (1:2 proportion of pulses and rice added to water with salt and tumeric), an evening meal of black tea with Sago Kheer (sweet pudding made with tapioca pearls or sabudana and milk), and a late dinner which replicated the lunch menu. Beyond the hospital environment, the typical Nagpurian diet is vegetarian predominant and consists of a diverse mix of fruits, vegetables, grains, non-saturated fats and proteins. In contrast, the dietary repertoire of the rural Korku tribal participants is considerably narrower and typically consists of locally available plant-based foods rich in carbohydrates and high in fibre but low in protein content such as jowar ki roti made from millet flour and water in combination with various types of vegetable chutneys containing garlic, salt and green chillies. They generally feed twice daily, rarely consuming milk or meat, and usually eat the leftover food from the previous day.