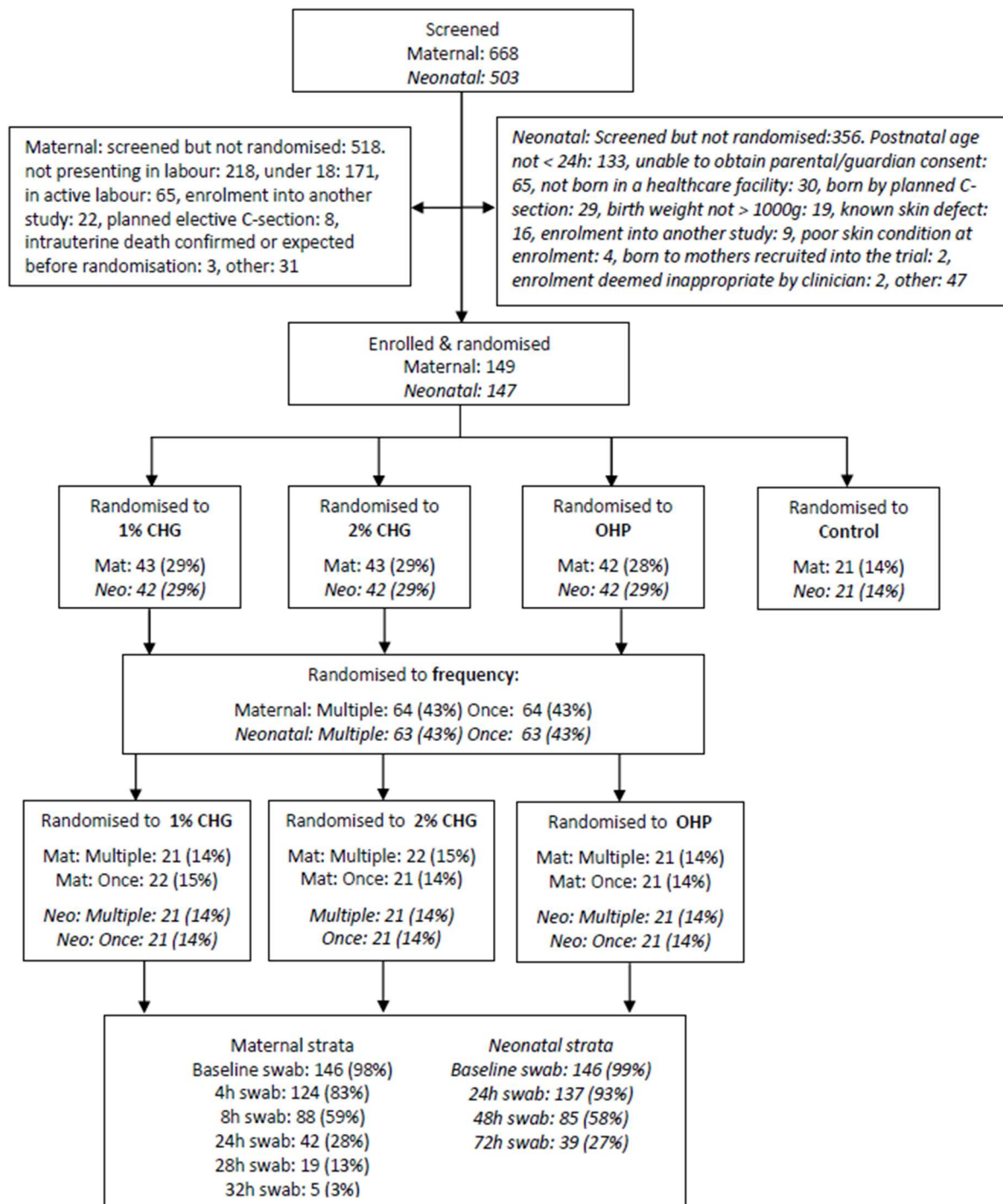


Safety and efficacy of antiseptic cleansing to reduce vertical transmission of multi-drug resistant pathogens to neonates (NeoVT-AMR)

Participant flow

Figure 1: CONSORT diagram for maternal and neonatal strata



Baseline Characteristics

Table 1. Participant baseline characteristics.

		Overall	1% CHG (N=43)	2% CHG (N=43)	OHP (N=42)	Once (N=64)	Multiple (N=64)	SOC (N=21)
Maternal stratum								
Age at randomisation (years)	Mean (SD)	25.7 (5.9)	26.3 (6.6)	25.4 (6.1)	25.7 (5.6)	27.5 (6.6)	24.1 (5.0)	24.8 (5.0)
Estimated gestational age at labour	Mean (SD)	37.7 (1.5)	37.8 (1.3)	37.8 (1.6)	37.4 (1.4)	37.9 (1.2)	37.5 (1.6)	37.6 (1.9)
Antenatal care during pregnancy	N (%)	144 (97%)	43 (100%)	43 (100%)	37 (88%)	62 (97%)	61 (95%)	21 (100%)
Tuberculosis	N (%)	2 (1%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	2 (3%)	0 (0%)
HIV	N (%)	14 (9%)	5 (12%)	4 (9%)	4 (10%)	10 (16%)	3 (5%)	1 (5%)
Antibiotics during pregnancy	N (%)	26 (17%)	5 (12%)	10 (23%)	9 (21%)	13 (20%)	11 (17%)	2 (10%)
Antibiotics since admission	N (%)	5 (3%)	3 (7%)	0 (0%)	2 (5%)	3 (5%)	2 (3%)	0 (0%)
Total log ₁₀ CFU: baseline	Mean (SD)	6.3 (2.0)	6.2 (1.9)	6.3 (1.9)	6.6 (2.1)	6.4 (1.7)	6.3 (2.2)	6.0 (2.1)
Neonatal stratum								
Age at enrolment (hours)	Mean (SD)	10.3 (6.3)	10.8 (5.9)	10.6 (6.6)	9.4 (6.0)	10.3 (6.1)	10.3 (6.3)	10.6 (7.2)
Estimated gestational age at labour (weeks)	Mean (SD)	36.7 (3.1)	36.9 (2.9)	36.6 (3.1)	37.0 (3.1)	36.5 (3.0)	37.2 (3.0)	36.0 (3.1)
Sex	Female	64 (44%)	17 (40%)	21 (50%)	17 (40%)	26 (41%)	29 (46%)	9 (43%)
	Male	82 (56%)	24 (57%)	21 (50%)	25 (60%)	37 (59%)	33 (52%)	12 (57%)
	Unknown	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Birth weight (g)	Mean (SD)	2729 (712)	2661 (671)	2751 (731)	2877 (724)	2739 (690)	2787 (732)	2528 (713)
Where admitted	Nursery	50 (34%)	14 (33%)	17 (40%)	13 (31%)	24 (38%)	20 (32%)	6 (29%)
	Nursery HDU	50 (34%)	13 (31%)	11 (26%)	16 (38%)	20 (32%)	20 (32%)	10 (48%)
	Postnatal ward with Mother	46 (31%)	14 (33%)	14 (33%)	13 (31%)	19 (30%)	22 (35%)	5 (24%)
	Unknown	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)

		Overall	1% CHG (N=43)	2% CHG (N=43)	OHP (N=42)	Once (N=64)	Multiple (N=64)	SOC (N=21)
Reason for admission	Birth asphyxia	48 (33%)	13 (31%)	12 (29%)	16 (38%)	20 (32%)	21 (33%)	7 (33%)
	Other	54 (37%)	15 (36%)	17 (40%)	13 (31%)	25 (40%)	20 (32%)	9 (43%)
	Routine admission	44 (30%)	13 (31%)	13 (31%)	13 (31%)	18 (29%)	21 (33%)	5 (24%)
	Unknown	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Any antibiotics prescribed before enrolment since birth	Yes	31 (21%)	8 (19%)	7 (17%)	10 (24%)	12 (19%)	13 (21%)	6 (29%)
	No	115 (78%)	33 (79%)	35 (83%)	32 (76%)	51 (81%)	49 (78%)	15 (71%)
	Unknown	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Chlorhexidine cord care given	Yes	112 (76%)	32 (76%)	32 (76%)	33 (79%)	50 (79%)	47 (75%)	15 (71%)
	No	34 (23%)	9 (21%)	10 (24%)	9 (21%)	13 (21%)	15 (24%)	6 (29%)
	Unknown	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Mother received antibiotics in labour	Yes	59 (40%)	16 (38%)	20 (48%)	18 (43%)	29 (46%)	25 (40%)	5 (24%)
	No	77 (52%)	25 (60%)	19 (45%)	21 (50%)	31 (49%)	34 (54%)	12 (57%)
	Unknown	11 (7%)	1 (2%)	3 (7%)	3 (7%)	3 (5%)	4 (6%)	4 (19%)
Total log ₁₀ CFU: baseline	Mean (SD)	4.3 (2.9)	4.2 (2.8)	4.3 (3.1)	3.9 (2.8)	3.9 (2.5)	4.4 (3.2)	5.3 (3.4)

Individuals assigned to non-standard of care (SOC) arm appear twice in the table: in the randomised antiseptic and frequency. One neonate in the neonatal stratum was withdrawn before any baseline data were collected and is shown as unknown.

Outcome Measures

Table 2. Maternal efficacy outcomes.

Arm	Change baseline to 4h log ₁₀ CFU mean (SD) [N]	Change baseline to 8h log ₁₀ CFU mean (SD) [N]	Change baseline to 24h log ₁₀ CFU mean (SD) [N]	Change baseline to 28h log ₁₀ CFU mean (SD) [N]	Change baseline to log ₁₀ CFU 32h mean (SD) [N]	Modelled effect size log ₁₀ CFU (95% CI)	p-value	Overall p-value of antiseptic
<i>Total log₁₀ CFU</i>								
1% CHG (N=43)	-4.5 (2.3) [35]	-4.3 (2.6) [22]	-2.5 (2.5) [15]	-4.1 (2.1) [6]	-4.7 (3.0) [2]	<0.0001
2% CHG (N=43)	-5.2 (2.2) [37]	-5.0 (2.7) [28]	-4.3 (3.1) [12]	-2.5 (1.0) [3]	-1.7 (NA) [1]	-0.6 (-1.4, 0.2)	0.12	
OHP (N=42)	-2.7 (2.2) [36]	-3.1 (2.2) [27]	-2.4 (3.7) [10]	-3.3 (4.0) [6]	-7.6 (NA) [1]	1.7 (0.9, 2.5)	<0.0001	
Once (N=64)	-4.3 (2.4) [56]	-3.7 (2.9) [36]	-2.2 (2.6) [18]	-2.3 (1.7) [8]	-4.7 (3.0) [2]	
Multiple (N=64)	-4.0 (2.6) [52]	-4.6 (2.3) [41]	-3.8 (3.4) [19]	-4.7 (3.3) [7]	-4.6 (4.1) [2]	-0.4 (-1.1, 0.2)	0.20	
SOC (N=21)	0.2 (1.4) [14]	-0.5 (1.7) [10]	-0.3 (2.3) [5]	0.5 (2.5) [4]	1.9 (NA) [1]	3.5 (2.4, 4.6)	<0.0001	
<i>Gram negative log₁₀ CFU</i>								
1% CHG (N=43)	-2.5 (2.3) [35]	-2.5 (2.7) [22]	-1.5 (3.3) [15]	-2.7 (2.7) [6]	-2.2 (3.1) [2]	0.0006
2% CHG (N=43)	-2.5 (2.4) [37]	-2.0 (2.9) [28]	-1.0 (2.6) [12]	-1.4 (1.5) [3]	-0.6 (NA) [1]	-0.1 (-0.8, 0.6)	0.72	
OHP (N=42)	-1.8 (2.6) [36]	-1.9 (2.2) [27]	-0.4 (2.6) [10]	-1.7 (3.6) [6]	-2.7 (NA) [1]	1.1 (0.4, 1.8)	0.0023	
Once (N=64)	-2.3 (2.3) [56]	-1.5 (2.7) [36]	-0.7 (2.7) [18]	-1.9 (2.0) [8]	-2.2 (3.1) [2]	
Multiple (N=64)	-2.2 (2.6) [52]	-2.6 (2.4) [41]	-1.3 (3.0) [19]	-2.3 (3.7) [7]	-1.7 (1.5) [2]	-0.1 (-0.7, 0.5)	0.72	
SOC (N=21)	-0.3 (1.7) [14]	0.1 (1.4) [10]	1.1 (1.5) [5]	2.1 (4.4) [4]	4.8 (NA) [1]	2.1 (1.1, 3.0)	<0.0001	
<i>Neonate born to mother: Total log₁₀ CFU</i>								
1% CHG (N=43)	2.9 (3.1) [36]	0.019
2% CHG (N=43)	2.5 (2.6) [38]	-0.4 (-1.8, 1.0)	0.54	
OHP (N=42)	4.4 (3.6) [37]	1.5 (0.1, 2.9)	0.038	
Once (N=64)	3.3 (3.2) [56]	
Multiple (N=64)	3.3 (3.3) [55]	-0.0 (-1.2, 1.1)	0.99	
SOC (N=21)	3.5 (2.4) [17]	0.5 (-1.4, 2.4)	0.58	

Arm	Change baseline to 4h log ₁₀ CFU mean (SD) [N]	Change baseline to 8h log ₁₀ CFU mean (SD) [N]	Change baseline to 24h log ₁₀ CFU mean (SD) [N]	Change baseline to 28h log ₁₀ CFU mean (SD) [N]	Change baseline to log ₁₀ CFU 32h mean (SD) [N]	Modelled effect size log ₁₀ CFU (95% CI)	p-value	Overall p-value of antiseptic
<i>Skin score</i>								
1% CHG (N=43)	0.19 (0.52) [36]	0.09 (0.68) [22]	-0.21 (0.43) [14]	-0.50 (0.55) [6]	-0.50 (0.71) [2]			0.021
2% CHG (N=43)	0.32 (0.53) [37]	0.22 (0.51) [27]	0.38 (0.65) [13]	0.00 (0.00) [3]	0.00 (NA) [1]	0.16 (-0.03, 0.35)	0.09	
OHP (N=42)	0.46 (0.56) [37]	0.32 (0.55) [28]	0.00 (0.47) [10]	0.17 (0.41) [6]	1.00 (NA) [1]	0.26 (0.07, 0.45)	0.0067	
Once (N=64)	0.30 (0.57) [56]	-0.03 (0.45) [36]	-0.16 (0.37) [19]	-0.25 (0.46) [8]	-0.50 (0.71) [2]			
Multiple (N=64)	0.35 (0.52) [54]	0.44 (0.59) [41]	0.28 (0.67) [18]	0.00 (0.58) [7]	0.50 (0.71) [2]	0.21 (0.06, 0.36)	0.0079	..
SOC (N=21)	0.07 (0.27) [14]	0.00 (0.00) [10]	0.00 (0.00) [5]	0.00 (0.00) [4]	0.00 (NA) [1]	-0.04 (-0.31, 0.22)	0.74	..

Primary and key secondary outcomes with modelled effect sizes averaged across both days. Estimates are presented vs 1% CHG applied once.

Table 3. Neonatal efficacy outcomes.

Arm	Baseline mean (SD) [N]	Change baseline to 24h mean (SD) [N]	Change baseline to 48h mean (SD) [N]	Change baseline to 72h mean (SD) [N]	Modelled effect size (95% CI)	p-value	Overall p-value of antiseptic
<i>Total log₁₀ CFU</i>							
1% CHG (N=42)		1.1 (2.8) [39]	1.8 (3.3) [24]	3.5 (3.3) [6]	0.064
2% CHG (N=42)		0.9 (2.9) [37]	2.5 (2.9) [21]	2.7 (3.6) [9]	-0.2 (-1.1, 0.7)	0.63	
OHP (N=42)		2.0 (3.8) [39]	3.5 (3.2) [26]	4.1 (2.9) [15]	0.7 (-0.2, 1.6)	0.11	
Once (N=63)		1.5 (2.7) [58]	3.0 (3.3) [35]	4.7 (2.2) [18]
Multiple (N=63)		1.3 (3.7) [57]	2.3 (3.1) [36]	1.9 (3.5) [12]	-0.5 (-1.2, 0.2)	0.17	
SOC (N=21)		2.0 (3.8) [20]	2.7 (3.5) [14]	3.8 (3.7) [9]	1.3 (0.2, 2.4)	0.017	
<i>Gram negative log₁₀ CFU</i>							
1% CHG (N=42)		1.8 (2.8) [39]	2.1 (1.8) [24]	4.3 (1.9) [6]	0.86
2% CHG (N=42)		1.3 (2.8) [39]	2.2 (3.1) [21]	3.1 (1.9) [9]	-0.1 (-1.1, 0.8)	0.79	
OHP (N=42)		1.5 (3.0) [39]	2.3 (3.4) [26]	2.3 (2.4) [15]	-0.3 (-1.2, 0.7)	0.59	
Once (N=63)		1.6 (2.6) [59]	2.5 (3.3) [35]	2.4 (2.0) [18]
Multiple (N=63)		1.4 (3.1) [58]	1.9 (2.3) [36]	3.7 (2.4) [12]	-0.1 (-0.8, 0.7)	0.87	
SOC (N=21)		0.4 (2.3) [20]	0.6 (4.0) [14]	1.4 (4.0) [9]	-0.9 (-2.1, 0.3)	0.14	
<i>Skin score</i>							
1% CHG (N=42)		-0.13 (0.47) [39]	-0.08 (0.58) [24]	0.00 (0.00) [7]	0.90
2% CHG (N=42)		-0.10 (0.38) [39]	-0.14 (0.36) [21]	-0.22 (0.44) [9]	0.02 (-0.15, 0.18)	0.86	
OHP (N=42)		-0.05 (0.56) [39]	-0.12 (0.59) [26]	-0.13 (0.52) [15]	0.04 (-0.13, 0.20)	0.66	
Once (N=63)		-0.15 (0.52) [59]	-0.17 (0.57) [35]	-0.16 (0.50) [19]
Multiple (N=63)		-0.03 (0.42) [58]	-0.06 (0.47) [36]	-0.08 (0.29) [12]	0.02 (-0.12, 0.16)	0.78	
SOC (N=21)		-0.15 (0.37) [20]	-0.07 (0.27) [14]	-0.22 (0.44) [9]	-0.05 (-0.27, 0.16)	0.63	

Arm	Baseline mean (SD) [N]	Change baseline to 24h mean (SD) [N]	Change baseline to 48h mean (SD) [N]	Change baseline to 72h mean (SD) [N]	Modelled effect size (95% CI)	p-value	Overall p-value of antiseptic
<i>Temperature</i>							
1% CHG (N=42)	-0.2 (0.4) [24]	-0.2 (0.3) [11]	-0.2 (0.3) [6]	-0.2 (0.2) [3]	0.76
2% CHG (N=42)	-0.2 (0.3) [25]	-0.2 (0.3) [12]	-0.2 (0.2) [6]	-0.5 (0.1) [2]	0.0 (-0.1, 0.2)	0.67	
OHP (N=42)	-0.3 (0.3) [26]	-0.1 (0.3) [13]	-0.3 (0.3) [8]	-0.4 (0.2) [2]	-0.0 (-0.1, 0.1)	0.97	
Once (N=63)	-0.2 (0.3) [39]	
Multiple (N=63)	-0.3 (0.4) [36]	-0.2 (0.3) [36]	-0.3 (0.3) [20]	-0.3 (0.2) [7]	-0.1 (-0.2, 0.1)	0.41	..

Primary and key secondary outcomes with modelled effect sizes averaged across both days. Estimates are presented vs 1% CHG applied once.

Adverse Events

4.9 Line listing of SAEs

Maternal SAEs

Note: no mothers experienced multiple SAEs

SAE Ref	Trial Arm	First IMP	Last IMP	Date of onset	Main Diagnosis	Severity	Relatedness	Event Outcome	Date Resolved
1	CHG 1% Multiple	2022-05-23 09:30	2022-05-23 17:30	2022-05-24	Birth asphyxia	Grade 5 (Death)	Unrelated	Death	2022-05-25
2	CHG 1% Once	2022-05-25 09:00	2022-05-25 13:12	2022-05-25	Post partum haemorrhage	Grade 2 (Moderate)	Unrelated	Resolved	2022-05-25
3	CHG 1% Once	2022-06-06 08:58	2022-06-06 12:55	2022-06-06	Neonatal Intrauterine Death (fresh still birth) due to missed Transverse Lie	Grade 5 (Death)	Unrelated	Death	2022-06-07
4	SOC	2022-06-07 09:05	2022-06-07 17:02	2022-06-07	Neonatal Sepsis	Grade 5 (Death)	Unrelated	Death	2022-06-14
5	CHG 2% Once	2022-09-14 09:15	2022-09-14 09:15	2022-09-16	Congenital Abnormality	Grade 2 (Moderate)	Unrelated	Resolved with sequelae	2023-03-24
6	OHP Once	2022-11-16 08:55	2022-11-16 08:55	2022-11-16	Neonatal sepsis	Grade 5 (Death)	Unlikely to be related	Death	2022-11-18
7	CHG 2% Multiple	2022-12-05 08:53	2022-12-05 16:52	2022-12-06	Stillbirth	Grade 5 (Death)	Unrelated	Death	2023-02-10

CHG = chlorhexidine; IMP = investigational medicinal product; OHP = octenidine 0.1% combined with phenoxyethanol 2%; SAE = serious adverse event; SOC = standard of care

Neonatal SAEs

SAE Ref	SAE num	Trial Arm	First IMP	Last IMP	Date of onset	Main Diagnosis	Severity	Relatedness	Event Outcome	Date Resolved
1	1	CHG 2% Once	2022-03-07 11:30	2022-03-07 11:30	2022-03-31	Pneumonia	Grade 2 (Moderate)	Unrelated	Resolved	2022-04-08
2	1	CHG 2% Multiple	2022-03-22 15:35	2022-03-23 15:22	2022-03-24	Neonatal sepsis	Grade 2 (Moderate)	Unrelated	Resolved	2022-03-27
3	1	OHP Multiple	2022-03-22 15:45	2022-03-23 15:30	2022-03-24	Neonatal sepsis	Grade 2 (Moderate)	Unrelated	Resolved	2022-03-27
4	1	SOC			2022-06-14	Neonatal Sepsis	Grade 5 (Death)	Unrelated	Death	2022-06-18
5	1	CHG 2% Once	2022-06-14 11:04	2022-06-14 11:04	2022-06-16	Neonatal sepsis	Grade 3 (Severe)	Unrelated	Resolved	2022-06-27
5	2	CHG 2% Once	2022-06-14 11:04	2022-06-14 11:04	2022-06-17	hypoxic ischaemic encephalopathy	Grade 3 (Severe)	Unrelated	Resolved with sequelae	2022-06-27
6	1	CHG 1% Multiple	2022-06-28 16:40	2022-06-28 16:40	2022-06-29	Birth asphyxia	Grade 5 (Death)	Unrelated	Death	2022-06-30
7	1	CHG 2% Once	2022-06-28 11:32	2022-06-28 11:32	2022-06-29	hypoxic ischaemic encephalopathy	Grade 4 (Life- threatening)	Unrelated	Death	2022-07-01
8	1	CHG 1% Multiple	2022-09-13 11:21	2022-09-16 11:22	2022-09-20	Neonatal sepsis (Klebsiella pneumoniae)	Grade 2 (Moderate)	Unrelated	Death	2022-09-25
9	1	CHG 1% Once	2023-01-09 09:48	2023-01-09 09:48	2023-01-10	Neonatal sepsis	Grade 5 (Death)	Unrelated	Death	2023-03-24
10	1	SOC			2023-01-11	Respiratory distress syndrome	Grade 5 (Death)	Unrelated	Death	2023-01-11
11	1	SOC			2023-02-16	Neonatal death secondary to severe hypoxic ischaemic encephalopathy	Grade 5 (Death)	Unrelated	Death	2023-02-17

CHG = chlorhexidine; IMP = investigational medicinal product; OHP = octenidine 0.1% combined with phenoxylethanol 2%; SAE = serious adverse event; SOC = standard of care