Relationship Between COVID-19 Lockdown and Epidemiology of Neonatal Sepsis

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Background: We compared the hospital-based epidemiology of neonatal sepsis after the coronavirus disease 2019 lockdown (LD) versus historical epochs and the LD period versus phases of unlocking.

Methods: This retrospective cohort study was conducted in a level 3 neonatal unit. We compared neonates born in three 24-week periods—Group *LD*: 22 March 2020 to 5 September 2020—the reference group, Group *pre-LD*: 29 September 2019 to 14 March 2020 and Group temporally corresponding to LD in 2019 (*corres-LD*): 24 March 2019 to 7 September 2019. We also studied linear trends from LD phase 1.0 until Unlock 4.0. The key outcome was culture-positive sepsis.

Results: There were 1622, 2744 and 2700 subjects in groups *LD*, *pre-LD* and *corres-LD*, respectively. The incidence of any culture-positive sepsis in *pre-LD* was higher than *LD* [odds ratio (95% CI) = 1.61 (1.02–2.56)]. This was mainly due to a statistically significant reduction in *Acinetobacter baumannii* sepsis, with incidence rate differences of *pre-LD* versus *LD* [0.67 (95% CI: 0.37–0.97), $P = 0.0001$] and *corres-LD* versus *LD* [0.40 (95% CI: 0.16–0.64), $P = 0.0024$]. Groups *pre-LD* and *corres-LD* had higher proportion of multi-drug resistant (MDR)/extreme drug resistance/pan drug resistance sepsis than *LD* [77%, 77% and 44%, respectively (*P* values of both groups vs. *LD* = 0.01)]. From LD 1.0 to unlock 4.0, there were fewer episodes of MDR sepsis ($P_{\text{linear trends}} = 0.047$). On multivariable analysis, group *pre-LD* (vs. reference group *LD*), male sex, birth weight and Apgar score independently predicted culture-positive sepsis.

Conclusions: LD favorably impacted the epidemiology of neonatal sepsis in a hospital setting, with less *A. baumannii* and MDR sepsis, which persisted during unlocking.

Key Words: SARS-CoV-2, *Acinetobacter baumannii*, septicemia, multidrug resistant, newborn

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The coronavirus disease 2019 (COVID-19) pandemic has directly afflicted millions globally.[1] The pandemic has also caused collateral damage from other diseases.[2–4] A recent meta-analysis identified increased stillbirths, maternal deaths and postnatal depression during the pandemic.[5] Conversely, COVID-19–related restrictions have decreased the incidence of several non–COVID-19 viral diseases.[6–11] Respiratory viral infections decreased after the pandemic, despite more testing for viral illnesses.[12] To date, there are no reports regarding the effect of the COVID-19 pandemic on the changing epidemiology of neonatal sepsis.

Ours is a level III Neonatology Unit in a public-sector university hospital in northwest India. We deliver >6000 liveborn infants annually, of which ≈40% are preterm and ≈35% small for gestational age. Like other busy public-sector units in developing countries, neonatal sepsis is a major problem. 2%–3% of neonates in our unit develop culture-positive sepsis (unpublished 5-year unit data). Etiologic organisms include *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and coagulase-negative *Staphylococcus*, in that order. Multi-drug resistant (MDR) sepsis is common, like other parts of South Asia.[13]

In the absence of regionalized care, our center is overburdened with sick neonates. We have a 16-bedded neonatal intensive care unit (NICU) and a 24-bedded high dependency unit (HDU). We are often unable to immediately transfer neonates requiring NICU or HDU care to the respective facilities, owing to nonavailability of vacant beds, nor can we transfer out such patients. Consequently, we manage several neonates in the labor room stabilization unit- an interim high-dependency nursery- until such time that a transfer to the NICU or HDU is feasible. A surge in the delivery rate is a surrogate for overcrowding, and we have earlier anecdotally observed an increase in sepsis rates with overcrowding.

The government of India announced a public curfew on March 22, 2020, severe restrictions on March 23–24 and a stringent lockdown (LD) starting from March 25, 2020. The LD was extended until May 31, followed by unlocking in 1-month phases, during which restrictive measures were eased.

As expected, there were fewer neonates delivered in our center from March 22, 2020 onwards. A few months into the pandemic, we observed a decrease in episodes of culture-positive sepsis. In the absence of formal analysis of data, we were unsure about the validity of this observation and whether it was a consequence of fewer admissions, behavioral changes, administrative measures or a combination thereof. Improvements in the pattern of neonatal sepsis may hold useful lessons for a future non-pandemic situation.

Hence, we studied neonates delivered in 3 time periods, each lasting 6 months—the first starting with the LD in 2020, the second immediately prior to the LD and the third in 2019, temporally identical to the LD. We investigated trends across the phases of locking and unlocking. We hypothesized that the LD was associated with a lower incidence of neonatal sepsis, especially MDR sepsis and that unlocking was associated with a partial reversal of the same.

METHODS

We conducted a retrospective cohort study on neonates delivered in our hospital in three 24-week periods (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E680):

Group *LD*: 22 March 2020 to 5 September 2020.

Group *pre-LD*: prior to the LD: 29 September 2019 to 14 March 2020.

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Group temporally corresponding to LD in 2019 (*corres-LD*): 24 March 2019 to 7 September 2019.

Group *LD* was the reference group. We included Group *corres-LD* to control for the possible impact of seasonal variations on demographics and sepsis.

To study the effect of stringency of measures, we included all liveborn infants delivered from 22 March 2020 to 30 September 2020 (see Figure, Supplemental Digital Content 1; http://links.lww.com/INF/E680). A composite objective measure of restrictions is the Government Stringency Index, ranging from 0 to 100, with 100 representing maximum stringency.[14] This part of the study included the following phases:

Phase of LD/ Unlocking	Duration (mm/dd/yyyy)	Government Stringency Index
LD phases 1 and 2	March 22, 2020–May 3, 2020	96.3–100
LD phases 3 and 4	May 4, 2020–May 31, 2020	79.17–81.94
Unlock 1.0	June 1, 2020–June 30, 2020	75.46–76.39
Unlock 2.0	July 1, 2020–July 31, 2020	74.07–77.78
Unlock 3.0	August 1, 2020–August 31, 2020	79.63
Unlock 4.0	September 1, 2020–September 30, 2020	73.61–81.02

The time period of LD/unlocking was almost identical to Group *LD*, except that the former extended to 30 September 2020, whereas the latter ended on 5 September 2020. Detailed descriptions of the containment measures can be accessed elsewhere.[15]

We recorded demographic data, admission to the NICU and/or HDU, duration of hospital stay, the final outcome and sepsis data during hospital stay. Antibiotic resistance was defined as "no MDR," MDR, extreme drug resistance (XDR) and pan drug resistance (PDR).[16] In Group LD, we performed a COVID-19 GeneXpert test in all laboring mothers and isolated the neonates from their mothers and other neonates until the mother was reported negative. We recorded the number of neonates thus isolated, and the number of neonates and mothers whose test was positive.

We used χ^2 test, Fisher exact test, Mann-Whitney *U* or Student *t* test as appropriate. We calculated incidence rate ratios of episodes of culture-positive, *A. baumannii* and antibiotic-resistant sepsis. We compared the phases of LD/unlocking by tests for linear trends [χ^2 for linear trends, Jonkheere-Terpstra or Analysis of Variance for trends, as appropriate] and without linear trends (χ^2, Kruskal-Wallis test or Analysis of Variance, as appropriate). We performed a multivariable logistic regression to predict "any episode of culture-positive sepsis," with the following predictors selected *a priori*: Groups (Group *LD*: reference group), number of live births in the week that the subject was born (as a surrogate for overcrowding), sex, gestational age in weeks, birth weight in grams, 5-minute Apgar score and appropriateness for gestation. We tested for multi-collinearity using variance inflation factor and Eigenvalues. We included a constant and forced all variables into the model. We used SPSS v23 and Stata v14.2 for statistical analysis. As recruitment was based on time periods, we did not perform a formal sample size calculation.

RESULTS

There were 1622, 2744 and 2700 inborn neonates in groups *LD*, *pre-LD* and *corres-LD*, respectively (Table 1). Fewer neonates in group *pre-LD* and *corres-LD* were admitted in the NICU and HDU and at significantly higher postnatal ages. Neonates with gestational age <32 weeks in group *pre-LD* and *corres-LD* had shorter hospital stay. Compared with group *LD*, a significantly lower proportion in group *pre-LD* was discharged home alive.

Group *pre-LD* had a significantly higher proportion of neonates with any episode of culture-positive sepsis compared with group *LD* [odds ratio = 1.61 (95% CI: 1.02–2.56)], but not so in the case of *corres-LD* (Table 2). Group *pre-LD* had a significantly higher incidence rate ratio (IRR) of culture-positive sepsis compared with group *LD* [1.77 (95% CI: 1.13–2.85)], but not when *corres-LD* was compared with group *LD*. There were significant differences in etiologic organisms between the groups. Of note, there were no episodes of *A. baumannii* sepsis in Group *LD*, whereas there were 19 (24%) and 11 (20.7%) episodes in groups *pre-LD* and *corres-LD*, respectively. The IRR of *A. baumannii* sepsis in group *pre-LD* or *corres-LD* versus *LD* could not be calculated as the denominator was zero. Hence the incidence rate differences were calculated which were statistically significantly different for *pre-LD* versus *LD* [0.67 (95% CI: 0.37–0.97)] and *corres-LD* versus *LD* [0.40 (95% CI: 0.16–0.64)].

There were significantly more episodes caused by MDR/XDR/PDR organisms in group *pre-LD* and *corres-LD* compared with *LD*. The IRR of episodes caused by organisms that were MDR or worse when comparing group *pre-LD* versus *LD* [3.08 (95% CI: 1.64–6.29)] and group *corres-LD* versus *LD* [2.14 (95% CI: 1.11–4.48)] were statistically significant. Significantly more culture-positive episodes were treated with colistin in group *pre-LD* compared with group *LD*. Almost all isolates of *A. baumannii* were MDR/XDR/PDR. The difference in MDR/XDR/PDR organisms between the phases was primarily driven by the difference in *A baumannii*. There were no significant differences in the proportion of non–*A. baumannii* MDR organisms (as a percentage of all sepsis) between LD, pre-LD and corres-LD.

In group *LD*, 425 neonates were briefly isolated from their mothers and other neonates until their mothers' COVID-19 report was available. One-hundred-eight severe acute respiratory syndrome coronavirus-2–positive mothers were isolated from other patients in a dedicated COVID building along with their neonates. Eight of these neonates were detected to be severe acute respiratory syndrome coronavirus-2 positive.

When comparing the phases of LD and unlocking, there were significant differences in gestational age and birth weight across phases, but no significant linear trends (Table 3). The proportion of subjects with any episode of culture-positive sepsis declined from LD phase 1.0 to unlock phase 4.0 but was not statistically significant. The difference in the proportion of etiologic organisms did not show a linear trend. There were progressively fewer episodes of MDR sepsis ($P_{\text{linear trend}} = 0.047$).

The candidate predictors in the multivariable analysis did not show multi-collinearity, hence all were included in the model. The Group (ie, *LD*, *pre-LD* and *corres-LD*), male sex, birth weight and Apgar score independently predicted the occurrence of any episode of culture-positive sepsis (Table 4). The prediction accuracy was 97.9% (assuming cases with >50% predicted probability were true sepsis) and the C-statistic was 0.85 (95% CI: 0.81–0.89).

To better understand *A. baumannii,* which had disappeared in group *LD*, we pooled data of the first episode of Gram-negative sepsis from groups *pre-LD* and *corres-LD* and compared *A. baumannii* versus other Gram-negative sepsis (see Table, Supplementary Digital Content 2, http://links.lww.com/INF/E681). On univariable analysis, *A baumannii* sepsis was associated with male sex, lower gestational age, lower birth weight and more concurrent births in the week the subject was born. In a multivariable logistic regression analysis to predict *A baumannii* sepsis among all cases with Gram-negative sepsis in the full study population (see Table, Supplementary Digital Content 3, http://links.lww.com/INF/E682), the only independent predictor was the number of concurrent births.

TABLE 1. Comparison of Demographic, Admission, and Discharge Data Between 3 Groups

Variable	LD Period: Group "LD" (N = 1622)	Immediate Previous Period: Group "Pre-LD" (N = 2744)	Corresponding Period In 2019: Group "Corres-LD" (N = 2700)	*P* Value: Group "LD" vs. "Pre-LD" (Reference Group = "LD")	*P* Value: Group "LD" vs. "corres-LD" (Reference Group = "LD")
Gestational age, weeks					
Median (1st, 3rd quartile)	37.0 (34.0, 38.0)	37.0 (35.0, 38.0)	37.0 (34.0, 38.0)	0.1	0.022
Mean (SD)	35.77 (3.2)	35.90 (3.1)	35.92 (3.1)		
Gestation categories*				0.2	0.049
Extremely preterm (<28 weeks)	44 (2.7)	68 (2.5)	65 (2.4)		
Very preterm (28–<32 weeks)	125 (7.7)	220 (8.0)	230 (8.5)		
Moderate to late preterm (32–<37 weeks)	574 (35.4)	880 (32.1)	844 (31.3)		
Term (37–41 weeks)	877 (54.1)	1572 (57.3)	1554 (57.6)		
Post-term (>41 weeks)	2 (0.1)	4 (0.1)	7 (0.3)		
Birth weight, grams, median (1st, 3rd quartile)	2480.0 (1896.75, 2874.25)	2470.0 (1915.0, 2862.0)	2480.0 (1900.0, 2890.0)	0.9	0.9
Birth weight categories*					
<1000 g	59 (3.6)	129 (4.7)	123 (4.6)	0.3	0.5
1000–1499 g	154 (9.5)	236 (8.6)	277 (10.3)		
1500–2499 g	599 (36.9)	1051 (38.3)	979 (36.3)		
2500–4200 g	809 (49.9)	1324 (48.3)	1318 (48.8)		
>4200 g	1 (0.1)	4 (0.1)	3 (0.1)		
Sex*					
Male	883 (54.4)	1418 (54.0)	1426 (52.8)	0.9	0.5
Female	737 (45.4)	1259 (45.9)	1268 (47.0)		
Ambiguous	2 (0.1)	4 (0.1)	6 (0.2)		
Appropriateness for gestational age*					
AGA	999 (64.5)	1713 (63.3)	1670 (61.9)	0.3	0.2
SGA	513 (33.1)	944 (34.9)	971 (36.0)		
LGA	37 (2.4)	50 (1.8)	57 (2.1)		
Apgar score at 5 min					
Median (1st, 3rd quartile)	7 (5, 8)	7 (6, 8)	7 (6, 8)	<0.001	<0.001
Mean (SD)	7.42 (1.6)	7.29 (1.6)	7.23 (1.5)		
Admitted in NICU*	177 (10.9)	184 (6.7)	213 (7.9)	<0.001 [OR, 0.59 (95% CI: 0.47–0.73,)]	0.001 [OR, 0.70 (95% CI: 0.57–0.86)]
Admitted in HDU*	297 (18.3)	313 (11.4)	265 (9.8)	<0.001 [OR, 0.57 (95% CI: 0.48–0.68)]	<0.001 [OR, 0.49 (95% CI: 0.41–0.58)]
Age transferred to NICU, d, median (1st, 3rd quartile)	2 (1, 3)	3 (2, 5)	3 (2, 5)	<0.001	<0.001
Age transferred to HDU, d, median (1st, 3rd quartile)	7 (4, 13)	8 (5, 14)	10 (5, 17)	0.003	<0.001
Duration of hospital stay among <32 weeks gestation, d, median (1st, 3rd quartile)	20 (4, 39)	10 (2, 30)	12 (3, 29)	0.001	0.005
Final outcome	N = 1622	N = 2744	N = 2694		
Discharged home	1553 (95.7)	2583 (94.1)	2541 (94.3)	0.028	0.13
Died	67 (4.1)	145 (5.3)	142 (5.3)		
LAMA or DOR	1 (0.1)	2 (0.1)	4 (0.1)		
Transferred elsewhere	1 (0.1)	14 (0.5)	7 (0.3)		

*Figures in brackets are percentages of the total subjects in the respective period.

AGA indicates appropriate for gestational age; DOR, discharged on request; LAMA, left against medical advice; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.

DISCUSSION

The number of live births in group *LD* was only 60% of the numbers in group *pre-LD* and *corres-LD*. The reduced number of live births in group *LD* was probably due to difficulties encountered by patients in traveling to our hospital during the LD and the fear of contracting COVID-19 at our hospital. Many mothers may have preferred to deliver in a hospital closer to home. Neonates in group *LD* had better Apgar scores and were discharged with better outcomes. Greater proportions in group *LD* were admitted in the NICU and HDU, and at a younger postnatal age. There was an overall reduction in culture-proven sepsis following the LD primarily driven by a striking reduction in *A. baumannii* sepsis and sepsis due to MDR/XDR/PDR organisms. This led to lower usage of colistin. Patients in the *pre-LD* group (compared with group *LD*), male sex, lower birth weight and Apgar score were independent predictors of any episode of culture-positive sepsis. It was reassuring to find that there was no increase in the incidence of culture-proven sepsis with progressive unlocking.

There were no clinically meaningful differences in the average gestation between the three groups, although there was a statistically significant difference between *LD* and *corres-LD*. Our observation is contrary to previous reports, where the incidence of preterm births has declined during the pandemic.[5,17] More neonates were admitted to the NICU and HDU after the LD possibly because the decrease in absolute number of live births made it easier to find a vacant bed in our NICU or HDU. The lower postnatal age of transfer to these areas supports the latter possibility. Similarly, the relatively longer hospital stay in the *LD* group can be attributed to the greater availability of vacant beds and hence less pressure on the physicians to discharge patients before schedule from the hospital.

TABLE 2. Comparison of Sepsis-Related Data Between 3 Groups

Variable	LD Period: Group "LD" (N = 1622)	Immediate Previous Period: Group "Pre-LD" (N = 2744)	Corresponding Period in 2019: Group "Corres-LD" (N = 2700)	*P* Value: Group "LD" vs. "Pre-LD" (Reference Group = "LD")	*P* Value: Group "LD" vs. "Corres-LD" (Reference Group = "LD")
Number of patients with any episode of culture-positive sepsis	25 (1.5)	68 (2.5)	51 (1.9)	0.038 [OR, 1.61 (95% CI: 1.02–2.56)]	0.4 [OR, 1.23 (95% CI: 0.76–2.00)]
Number of episodes of culture-positive sepsis*	N = 25	N = 68	N = 51		
1 episode	23 (92)	59 (86.8)	49 (96.1)	0.6	0.4
2 episodes	2 (8)	7 (10.3)	2 (3.9)		
3 episodes	0 (0)	2 (2.9)	0 (0)		
Total number of episodes of culture-positive sepsis	27	79	53	…	…
Cumulative duration of hospital stay, person-days	17,210	28,387	27,432	…	…
Incidence rate of culture-positive sepsis (episodes/1000 patient-days)	1.57	2.78	1.93	0.004 [IRR, 1.77 (95% CI: 1.13–2.85)]	0.19 [IRR, 1.23 (95% CI: 0.76–2.04)]
Number of episodes with specific organisms†	N = 27	N = 79	N = 53		
E. coli	4 (14.8)	11 (13.9)	9 (16.9)	0.03	0.049
K. pneumoniae	3 (11.1)	3 (3.8)	4 (7.5)		
A. baumannii	0 (0)	19 (24.0)	11 (20.7)		
S. aureus	0 (0)	5 (6.3)	0 (0)		
S. epidermidis	4 (14.8)	15 (18.9)	14 (26.4)		
Other CONS	7 (25.9)	16 (20.2)	8 (15.1)		
E fecalis/fecium	1 (3.7)	1 (1.3)	0 (0)		
Miscellaneous	8 (29.6)	9 (11.4)	7 (13.2)		
Incidence rate of *A baumannii* sepsis (episodes/1000 patient-days)	0	0.67	0.4	0.0001 [IR difference, 0.67 (95% CI: 0.37–0.97)]	0.0024 [IR difference, 0.40 (95% CI: 0.16–0.64)]
Incidence rate of non-*A baumannii* sepsis (episodes/1000 patient-days)	1.57	2.11	1.53	0.09 [IRR, 1.35 (95% CI: 0.84–2.21)]	0.46 [IRR, 0.98 (95% CI: 0.59–1.65)]
Antibiotic resistance among total number of episodes of sepsis†	N = 27	N = 79	N = 53		
Not MDR or worse	15 (55.5)	18 (22.8)	12 (22.6)	0.01	0.01
MDR	9 (33.3)	35 (44.3)	31 (58.5)		
XDR	3 (11.1)	25 (31.6)	10 (18.9)		
PDR	0 (0)	1 (1.3)	0 (0)		
Incidence rate of MDR or worse (episodes/1000 patient-days)	0.7	2.1	1.5	<0.001 [IRR, 3.08 (95% CI: 1.64, 6.29)]	0.007 [IRR, 2.14 (95% CI: 1.11, 4.48)]
Number of episodes of MDR or worse *A. baumannii* sepsis	0 (0†)	18 (22.8†) (94.7‡)	10 (18.9†) (90.1‡)	0.007	0.02
Number of episodes of MDR or worse non–*A. baumannii* sepsis†	12 (44.4)	43 (54.4)	31 (58.5)	0.37	0.23
Any culture-positive episode treated with meropenem*	19 (76.0)	59 (86.8)	44 (86.3)	0.2 [OR, 1.23 (95% CI: 0.47–3.23)]	0.3 [OR, 2.04 (95% CI: 0.69–6.25)]
Any culture-positive episode treated with colistin*	5 (20.0)	32 (47.1)	19 (37.3)	0.018 [OR, 3.03 (95% CI: 1.03–8.33)]	0.13 [OR, 2.44 (95% CI: 0.80–7.69)]
Patient care area where episodes of sepsis occurred†	N = 27	N = 79	N = 53		
Labor room stabilization	3 (11.1)	27 (34.2)	18 (33.9)	0.02	0.003
NICU	17 (62.9)	45 (56.9)	33 (62.3)		
HDU	7 (25.9)	7 (8.8)	2 (3.8)		
Age 1st episode of sepsis, d, median (1st, 3rd quartile)	5 (3, 13.5)	5 (3, 8)	6 (3, 9)	0.7	0.7
1st episode of sepsis categorized by time of onset*					
EONS	11 (44.0)	25 (36.8)	13 (25.5)	0.5 [OR for LONS = 1.35 (95% CI: 0.53–3.43)]	0.1 [OR for LONS = 2.30 (95% CI: 0.84–6.31)]
LONS	14 (56.0)	43 (63.2)	38 (74.5)		

*Percent expressed of number of patients with any episode of culture-positive sepsis.

†Percent expressed of total number of episodes of culture-positive sepsis.

‡Percent expressed of all episodes of *A. baumannii* sepsis.

CONS indicates coagulase-negative *Staphylococcus*; EONS, early-onset neonatal sepsis; IR, incidence rate; IRR, IR ratio; LONS, late-onset neonatal sepsis; OR, odds ratio.

The decrease in hospital deliveries coupled with an increase in the need for NICU/HDU care has not been reported before. However, a 57% decrease in children's emergency visits has been documented during the peak of the pandemic.[18–21] Like us, Goldman et al found that the acuity of sickness and admission rate among children was higher during the peak compared with preceding epochs. In a recent meta-analysis, Chmielewska et al did not observe significant differences in the mode of delivery, births <32 weeks gestation, perinatal asphyxia, low-birth-weight status, NICU admissions or neonatal deaths between the pandemic and pre-pandemic periods.[5] The incidence of preterm births <37 weeks gestation was significantly lower only among high-income countries. This meta-analysis did not evaluate neonatal sepsis.

The improvement in the epidemiology of neonatal sepsis in our study may be partly explained by earlier transfer of neonates to the NICU and HDU than what was possible prior to the LD. This

TABLE 3. Comparison of the Phases of Lockdown and Unlocking

Variables	Lockdown Phases 1 and 2 (N = 387)	Lockdown Phase 3 and 4 (N = 252)	Unlock Phase 1 (N = 310)	Unlock Phase 2 (N = 339)	Unlock Phase 3 (N = 296)	Unlock Phase 4 (N = 266)	*P* Value of Linear Trends*	*P* Value Without Linear Trends†
Number of live births per day, mean (SD)	8.9 (2.8)	9.0 (3.2)	10.3 (3.2)	10.9 (4.3)	9.6 (3.3)	8.8 (3.0)	0.7	0.067
Gestational age, weeks, median (1st, 3rd quartile)	37 (35, 38)	37 (34, 38)	36 (34, 38)	36 (34, 38)	37 (34, 38)	37 (34, 38)	0.6	0.028
Gestation categories‡								
Extremely preterm (<28 weeks)	8 (2.1)	10 (4.0)	10 (3.2)	8 (2.4)	7 (2.4)	7 (2.7)	0.3	0.059
Very preterm (28–<32 weeks)	17 (4.4)	22 (8.7)	28 (9.0)	31 (9.1)	23 (7.8)	26 (10.0)		
Moderate to late preterm§	130 (33.8)	82 (32.5)	120 (38.7)	128 (37.8)	104 (35.1)	76 (29.1)		
Term (37–41 weeks)	230 (59.7)	138 (54.8)	152 (49.0)	170 (50.1)	162 (54.7)	152 (58.2)		
Post-term (>41 weeks)	0	0	0	2 (0.6)	0	0		
Birth weight, grams, median (1st, 3rd quartile)	2521 (1975, 2897.5)	2500 (1862.25, 2930)	2325 (1748, 2721.5)	2523 (1910, 2878)	2512 (1907, 2918)	2444 (1900.75, 2878)	0.7	0.008
Birth weight categories‡								
<1000 g	10 (2.6)	12 (4.8)	13 (4.2)	14 (4.1)	9 (3.0)	12 (4.6)	0.3	0.056
1000–1499 g	22 (5.7)	31 (12.3)	37 (11.9)	32 (9.4)	26 (8.8)	27 (10.3)		
1500–2499 g	153 (39.7)	79 (31.3)	133 (42.9)	114 (33.6)	106 (35.8)	99 (37.9)		
2500–4200 g	199 (51.7)	130 (51.6)	127 (41.0)	179 (52.8)	155 (52.4)	123 (47.1)		
>4200 g	1 (0.3)	0	0	0	0	0		
Sex‡								
Male	213 (55.5)	141 (56.0)	178 (57.4)	178 (52.5)	151 (51.0)	149 (56.0)	0.7	0.4
Female	174 (45.0)	111 (44.0)	132 (42.6)	159 (46.9)	145 (49.0)	116 (43.6)		
Ambiguous	0 (0)	0 (0)	0 (0)	2 (0.6)	0 (0)	1 (0.4)		
Appropriateness for gestation‡								
AGA	221 (61.2)	169 (68.1)	185 (63.4)	210 (64.8)	194 (67.6)	157 (60.6)	0.9	0.4
SGA	130 (36.0)	77 (31.0)	99 (33.9)	107 (33.0)	84 (29.3)	97 (37.5)		
LGA	10 (2.8)	2 (0.8)	8 (2.7)	7 (2.2)	9 (3.1)	5 (1.9)		
Apgar score at 5 min	8 (7, 8)	8 (7, 8)	8 (7, 9)	8 (7, 8)	8 (7, 9)	8 (7, 8)	0.04	0.02
Admitted in NICU‡	36 (9.3)	26 (10.3)	37 (11.9)	39 (11.5)	34 (11.5)	13 (11.3)	0.3	0.9
Admitted in HDU‡	80 (20.7)	50 (19.8)	54 (17.4)	46 (13.6)	62 (20.9)	24 (9.0)	0.002	<0.001
Age transferred to NICU, d, median (1st, 3rd quartile)	2 (2, 2.75)	2 (1, 2.25)	2 (1.5, 3)	2 (1, 3)	3 (1, 5)	2 (1, 4.25)	0.13	0.4
Age transferred to HDU, d, median (1st, 3rd quartile)	4 (2, 8)	7 (3, 15)	9 (5, 12.25)	8 (5, 13)	7 (4, 15.25)	5.5 (2.25, 10)	0.018	0.001
Any episode of culture-positive sepsis‡	8 (2.1)	4 (1.6)	3 (1.0)	6 (1.8)	4 (1.4)	3 (1.1)	0.4	0.9
Total number of episodes with specific organisms	N = 9	N = 4	N = 4	N = 6	N = 4	N = 5		
E. coli	1	1	2	0	0	1	0.1	0.04
K. pneumoniae	0	0	0	1	2	0		
A. baumannii	0	0	0	0	0	2		
P. aeruginosa	0	0	0	1	1	0		
S. epidermidis	2	0	0	2	0	0		
Other CONS	2	3	1	1	0	1		
E fecalis/fecium	2	0	0	0	0	0		
Miscellaneous	2	0	1	1	1	1		
Antibiotic resistance among total number of episodes of sepsis	N = 9	N = 4	N = 4	N = 6	N = 4	N = 5		
Not MDR or worse	2	3	3	3	4	1	0.047	0.9
MDR	4	1	1	3	0	1		
XDR	3	0	0	0	0	3		
Culture-positive episode treated with meropenem¶	5 (62.5)	3 (75)	3 (100)	4 (66.7)	4 (100)	3 (100)	0.1	0.5
Culture-positive episode treated with colistin¶	1 (12.5)	0 (0)	2 (66.7)	2 (33.3)	0 (0)	1 (33.3)	0.5	0.2
Outcome‡								
Discharged home	370 (95.6)	241 (95.6)	297 (95.8)	323 (95.3)	285 (96.3)	252 (94.7)	0.6	0.7
Died	17 (4.4)	10 (4.0)	13 (4.2)	15 (4.4)	11 (3.7)	13 (4.9)		
LAMA or DOR	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)		
Transferred elsewhere	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.4)		

(*Continued*)

TABLE 3. (*Continued*.)

Variables	Lockdown Phases 1 and 2 (N = 387)	Lockdown Phase 3 and 4 (N = 252)	Unlock Phase 1 (N = 310)	Unlock Phase 2 (N = 339)	Unlock Phase 3 (N = 296)	Unlock Phase 4 (N = 266)	*P* Value of Linear Trends*	*P* Value Without Linear Trends†
Duration hospital stay, d, median (1st, 3rd quartile)	4 (3, 7)	5 (3, 7)	5 (4, 7)	4 (4, 7)	4 (3, 8)	4 (3, 7)	0.07	0.018
Duration of hospital stay among <32 weeks gestation, d, median (1st, 3rd quartile)	29 (10.5, 54.5)	18.5 (5, 41)	17.5 (2.75, 31.5)	20 (4, 29)	22 (3, 39)	29 (8, 57)	0.1	0.8

*χ^2 test for linear trends of outcome categorical variables. Jonckheere-Terpstra test for linear trends of outcome numerical variables.
†χ^2 test for outcome categorical variables. Kruskal-Wallis test for outcome numerical variables.
‡Percent expressed of total number in respective lockdown/unlock phase.
§32–<37 weeks.
¶Percent expressed out of total number of culture-positive episodes in respective lockdown/unlock phase.
AGA indicates appropriate for gestational age; CONS, coagulase-negative *Staphylococcus*; DOR, discharged on request; LAMA, left against medical advice; LGA, large for gestational age; SGA, small for gestational age.

is reflected in fewer episodes of sepsis in the labor room stabilization unit. The changes can also be attributed to behavioral factors. Unfortunately, we do not have data that can quantify these behavioral changes, so our observations are necessarily anecdotal and subjective. Prior to the LD, healthcare workers (HCW) and family members were expected to wash hands at entry to all patient care areas and HCWs were expected to follow hand hygiene measures at the 5 moments of hand hygiene prescribed by the World Health Organization but wearing a face mask was not mandatory. During the LD, compliance to hand hygiene measures increased substantially and there was universal usage of face masks by HCWs and family members. Before the LD, housekeeping measures included regular disinfection of equipment and surfaces, but during the LD these were followed more assiduously, with disinfection of high-contact surfaces such as door handles, telephones, etc. performed at least twice in every nursing shift. Instructions for disinfection of mobile phones were provided to all HCWs. Patients were distributed across more areas because those awaiting COVID reports were isolated in a separate 12-bedded isolation ward for mothers and a 6-bedded isolation ward for neonates, and proven cases were managed in a separate building. HCWs working in the isolation wards with suspected or proven cases of COVID-19 donned N-95 masks, caps, goggles, impervious gowns, shoe covers and gloves. There were no changes in the water sources or frequency of surveillance cultures for MDR organisms in the unit. Academic activities and meetings went online, and HCWs practiced social distancing.

TABLE 4. Multivariable Logistic Regression Model to Predict Patients With Any Episode of Culture-Positive Sepsis

Variable	Regression Coefficient	aOR	95% CI of aOR	*P* value
Constant	−2.25			
Time period				0.053
LD (reference group)				
Pre-LD	0.81	2.24	1.11–4.51	0.024
Corres-LD	0.51	1.67	0.83–3.35	0.15
Births in the week subject was born	−0.007	0.99	0.98–1.004	0.2
Male sex	0.81	2.26	1.55–3.29	<0.001
Gestational age	−0.05	0.95	0.48–1.08	0.5
Birth weight	−0.002	0.998	0.997–0.999	<0.001
Apgar score at 5 min	0.53	1.69	1.46–1.96	<0.001
Appropriateness for gestation				0.2
AGA (reference group)				
SGA	−0.4	0.67	0.39–1.16	0.15
LGA	0.92	2.5	0.64–9.73	0.19

AGA indicates appropriate for gestational age; aOR, adjusted odds ratio; LGA, large for gestational age; SGA, small for gestational age.

A. baumannii is an important cause of neonatal sepsis in developing countries.[22] The decrease in *A. baumannii* sepsis disproportionate to other Gram-negative sepsis in group *LD* is puzzling. The only independent risk factor we could identify was less overcrowding (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/E683), but it is unclear why it should preferentially impact one species. *A. baumannii* is known to behave differently than other Gram-negative bacteria, characterized by more rapid acquisition of MDR, and resistance to desiccation and disinfectants.[23] Compared with *E. coli* or *Klebsiella*, neonates with *A. baumannii* sepsis have lower birth weight.[24] It is possible that infection control measures may have differential effects on *A. baumannii* sepsis and other Gram-negative sepsis. In a systematic review and network meta-analysis of 42 studies on adult ICU patients, compared with standard treatment alone, the addition of environmental cleaning to standard treatment plus antibiotic stewardship program or the addition of source control to standard treatment and environmental cleaning significantly reduced MDR *A. baumannii* sepsis.[25] On the other hand, infection control strategies that mandatorily included antibiotic stewardship programs significantly reduced sepsis due to MDR extended-spectrum beta-lactamase producing Gram-negative infections. In a study from China, the authors reported the effect of relocation of the NICU and introduction of a care bundle for prevention of ventilator-acquired pneumonia (VAP).[26] The incidence of VAP due to *A. baumannii* decreased from 79% to 36%, whereas VAP due to *K. pneumoniae* increased from 17% to 18%. Infection control measures rapidly control outbreaks of *A. baumannii* in neonatal units.[27,28] Our study was not specifically designed to evaluate the effect of infection control measures on the decline of MDR sepsis or organism-wise sepsis and we were unable to quantify the infection control measures. Although augmentation in infection control measures was an important feature of the LD epoch, apart from infection control measures there were several other differences between the 3 epochs. Authors of a study on older patients in the United Kingdom reported differential effects of the pandemic on etiologic organisms: *Enterobacteriaceae* reached an all-time low and coagulase-negative *Staphylococcus* an all-time high.[29]

The absolute decline in MDR sepsis was not merely a consequence of overall decline in sepsis, as MDR sepsis as a proportion of all sepsis declined significantly in group *LD*. Our data shows that the decrease in MDR sepsis was driven by the decline in *A. baumannii,* which is frequently multi-drug resistant.

As early-onset neonatal sepsis is attributed to maternal risk factors that are unlikely to be altered by the pandemic, and late-onset neonatal sepsis is environmentally acquired, we expected to see a greater proportion of early-onset neonatal sepsis in group *LD*. We observed this difference, but it was not statistically significant.

It was interesting to note that there were no major differences from LD 1.0 to unlock 4.0. This could be due to the small sample sizes in each phase. The easing of restrictions may have had little impact on hospital functioning. It did not alter important predictors of sepsis, for example, gestational age, birth weight and appropriateness for gestational age. A closer look at the government stringency index shows that there was very little objective decline in the stringency of restrictions during the various phases of unlocking. We do not have data to quantify any change in behavior or infection control measures during the phases of unlocking.

In the multivariable analysis, Group *pre-LD* independently doubled the odds of an episode of culture-positive sepsis compared with group *LD*. Our analysis suggests that the overall changes after the LD were associated with less culture-positive sepsis rather than overcrowding specifically around the time of birth.

Groups *LD* and *corres-LD* covered virtually identical dates exactly a year apart whereas group *pre-LD* covered a different time of the year. Since the differences in most outcomes were larger between groups *LD* and *pre-LD* compared with groups *LD* and *corres-LD*, it suggests that seasonal differences may have accentuated the differences between Groups *LD* and *pre-LD*. We studied the incidence of sepsis, particularly *A. baumannii* sepsis, for 4 years prior to 2019, to evaluate the possibility that a downward sloping trend may have exaggerated the effect of the LD. However, no such trend could be observed from the year 2015 through 2018 (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/E683).

The strengths of our study were a large sample size and two comparison groups. Being retrospective, it was prone to several biases. There may have been unmeasured differences in patient characteristics, clinical practices, and rigor of data collection between the time periods. We limited our observation to hospital stay and may have missed cases of sepsis after transfer or discharge. Our results may not be generalizable to centers with fewer resource constraints, and less MDR sepsis. Weekly births are a sub-optimal surrogate for overcrowding. We were unable to quantify behavioral changes and infection control measures following the LD and during unlocking. We do not have data about the harm caused to neonates whose mothers were not able to reach our center due to the pandemic. Improvement in sepsis parameters may have occurred at the expense of worse outcomes among those who delivered elsewhere.

CONCLUSIONS

From the limited experience accrued from our center, we conclude that the LD may be associated with a decrease in culture-proven neonatal sepsis, primarily due to *A. baumannii* sepsis and antibiotic-resistant sepsis in settings like ours. Efforts must be made to consolidate the gains achieved during the pandemic by reinforcing the desirable administrative and infection control practices.

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Current Abstracts

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Imported Monkeypox From International Traveler, Maryland, United States, 2021

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Since the eradication of smallpox, monkeypox has assumed the role of the most prominent orthopoxvirus affecting human communities. Formerly a rare disease native to Africa, monkeypox is now endemic to countries in western and central Africa, which have faced a resurgence of monkeypox outbreaks over the past decade. Nigeria is in the midst of an ongoing monkeypox outbreak, as of October 2021, a total of 502 cases and 8 deaths from this disease had been reported. Outside Africa, cases of monkeypox remain rare, but are increasing: 7 international cases have been diagnosed since 2018. In the United States, a case was recently identified in Texas in a traveler returning from Nigeria. Before that case, the last confirmed monkeypox cases in the United States were in an outbreak involving 47 persons across 6 states; those cases were associated with contact of prairie dogs infected by imported rats from the Gambia. A case of imported monkeypox in Maryland, United States, and the infection control measures used to prevent additional disease transmission is described.

A 28-year-old man sought care for a diffuse vesicular rash that had developed over the preceding 24–48 hours. He had traveled on a flight from Lagos, Nigeria, and arrived in the United States the day he sought care. While in Nigeria, he visited relatives, stayed in hotel lodging without travel to rural regions and had no interactions with animals or animal carcasses. During his flight from Lagos, he noticed a burning sensation on his skin, followed by development of discrete vesicles on his forehead and nose, which spread to his arms, trunk and inner thighs over several hours. He denied having associated symptoms, including fever, chills or headache. On physical examination, right cervical lymphadenopathy and numerous 2–4 mm pustules on an erythematous base were noted. Some of the pustules had central umbilication and were present with acrofacial propensity.

The patient was given intravenous acyclovir for empiric treatment of disseminated varicella zoster virus infection, admitted and placed on contact and airborne isolation precautions. Within 24 hours of admission, no new lesions developed, and there was noticeable crusting of several existing vesicles. A 4-mm punch biopsy specimen from an intact pustule on the abdomen of the patient showed epidermal necrosis, reticular degeneration and vesiculation by staining with hematoxylin and eosin.

Based on the travel history of the patient and histopathologic findings, monkeypox was suspected, likely acquired by human contact in the absence of any animal exposures. Additional specimens of the skin lesions were identified by the Maryland Department of Health as nonvariola orthopox by real-time reverse transcription polymerase chain reaction and the Centers for Disease Control and Prevention (CDC) Laboratory Response Network protocol. CDC used viral culture and real-time reverse transcription polymerase chain reaction to confirm the diagnosis of monkeypox, further identifying the specimen as part of the West African clade, which has driven the outbreak in Nigeria since 2017.

Upon confirmation of the monkeypox diagnosis, all healthcare workers (HCWs) involved in the case were identified and 40 were classified as contacts by CDC guidelines. No HCW met the criteria for high-risk exposure, and no doses of preventive smallpox vaccine were administered. Disease transmission was not detected at the conclusion of the 21-day surveillance period.

Comment: Monkeypox has an overall case-fatality rate of up to 11%, and increasing human populations have no immunity to poxvirus; therefore, future progress in understanding monkeypox is critical. The World Health Organization Research and Development Blueprint in 2018 classified monkeypox as an emergent disease requiring accelerated research, development and public health action. Although the public health experience addressing monkeypox in the United States has been limited, this case illustrates the effectiveness of the basic principles of infection control; rapid identification and isolation of the index patient; use of personal protective equipment by HCWs; and thorough contact tracing, including monitoring for secondary cases throughout the incubation period.

Although vaccination was not required in this case, public health recommendations to prevent secondary disease transmission of monkeypox include the smallpox vaccine. The 2 Food and Drug Administration–approved vaccines are ACAM2000 and JYNNEOS; this second vaccine is a nonreplicating, live virus vaccine, licensed specifically for monkeypox prevention. In addition to smallpox vaccine, vaccinia immune globulin is available and can be used as prophylaxis for severely immunocompromised patients when smallpox vaccine should be avoided. The Food and Drug Administration–approved drugs to treat smallpox are tecovirimat and brincidofovir, which can also be used to treat monkeypox, but there are no monkeypox-specific antiviral drugs for treatment or postexposure prophylaxis.

Multiple appearances beyond disease-endemic countries indicate that monkeypox has become a relevant travel-related disease and physicians should remain vigilant in diagnosing and preventing transmission of this virus.