ORIGINAL ARTICLE

A Multicomponent Intervention to Improve Maternal Infection Outcomes

D. Lissauer,[1,2] L. Gadama,[3] C. Waitt,[1,4] S. Whyte,[1] G. Burnside,[5,6] A. Anilkumar,[6] R. Makuluni,[2] P. Okwaro,[4] L. Yang,[7] P. Waitt,[1,4,8] O. Musopole,[9] R. Bilesi,[9] B. Maseko,[2] J. Lwasa,[10] R. Mugahi,[11] C. Olaro,[11] M. Lamorde,[12] M. Makuta,[2] C. Kachiwaya,[2] T. Mkandawire,[2] A. Malunga,[2] N. Chitsulo,[2] P. Abitimo,[4] T. Ayabo,[4] A. Weeks,[1] J. Martin,[13] K. Hemming,[13] I. Gallos,[14] E.J.M. Monk,[15] J. Riches,[1] C. Chapuma,[2] J. Nanyondo S.,[16] F. Lorencatto,[17] M. Monahan,[18] B. Allegranzi,[19] C. Dunlop,[20] L. Atkins,[17] A. Rosala-Hallas,[6] T. Roberts,[18] C. Gamble,[6] A. Malata,[21] N. Desmond,[15] E. Kommwa,[22] A. Merriel,[1] W. Parry-Smith,[23,24] R. Smith,[1] I. Ndumu,[18] E. Williams,[18] B. Faque,[2] G. Banda,[2] A.L. Nyondo-Mipando,[1] A. Twimukye,[4] T. Chater,[6] A. Diplas,[6] V. Brizuela,[14] J.P. Souza,[25,26] J. Rylance,[27] J. Cheshire,[20] L. Hawker,[1] A. Coomarasamy,[28] and M. Bonet[14]

ABSTRACT

BACKGROUND

Maternal infection and sepsis are major causes of maternal death and severe illness worldwide, particularly in low- and middle-income countries. Inconsistent implementation of evidence-based recommendations for infection prevention and management and delays in detection and treatment of maternal sepsis contribute to the number of preventable deaths.

METHODS

We conducted a cluster-randomized trial to assess a multicomponent intervention, the Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) program. This program was designed to support health care providers in achieving three goals: adherence to World Health Organization (WHO) hand-hygiene standards; adoption of evidence-based practices for maternal infection prevention and management; and early detection of sepsis and use of the FAST-M (fluids, antibiotics, source control, transfer if required, and monitoring) treatment bundle. Usual care was provided in the control group, along with dissemination of guidelines. The primary outcome was a composite of infection-related maternal death, infection-related near-miss event (events in which women survived a life-threatening complication), or severe infection-related illness (deep surgical-site, deep perineal, or body-cavity infection) among women who were pregnant or had recently been pregnant.

RESULTS

We randomly assigned 59 health facilities (where 431,394 women gave birth during the trial) in Malawi and Uganda to the intervention group (30 clusters) or the usual-care group (29 clusters). A primary-outcome event occurred in 1.4% of the patients in the intervention group and in 1.9% of those in the usual-care group (risk ratio, 0.68; 95% confidence interval, 0.55 to 0.83; P<0.001). This effect was generally consistent between countries and among facilities of difference sizes and was sustained over time.

CONCLUSIONS

Implementation of the APT-Sepsis program led to a significantly lower risk of a composite of infection-related maternal death, infection-related near-miss event, or severe infection-related illness than usual care. (Funded by the Joint Global Health Trials scheme and others; APT-Sepsis ISRCTN number, ISRCTN42347014.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. David Lissauer can be contacted at david.lissauer@liverpool.ac.uk or at Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool Women's Hospital, Crown St., Liverpool, L8 7SS, United Kingdom.

This article was published on November 19, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2512698

Maternal infection is an important cause of maternal illness and death worldwide. It is associated with as many as half of in-hospital maternal deaths, with the greatest burden observed in low- and middle-income countries.[1-3] Infections during and after pregnancy are also associated with long-term illness in women and with adverse perinatal outcomes, such as stillbirth and neonatal death.[4-8] Outcomes are particularly poor in cases involving maternal sepsis.[9]

Global initiatives have identified the prevention and management of maternal infection and sepsis as a priority.[10-13] Several upstream deficiencies in care are critical contributors to maternal death from sepsis, including inconsistent adherence to infection-prevention practices, inappropriate use of antibiotic agents, and delays in the recognition and treatment of infection and sepsis.[3,14-16] These shortcomings are compounded by systemic constraints, such as inadequate staffing, overcrowded facilities, and limited supplies of key resources.[17,18]

The World Health Organization (WHO) has issued recommendations on adherence to hand-hygiene standards and evidence-based practices to prevent and treat maternal infection.[19-21] However, adherence to these recommendations is suboptimal.[3,14] The use of structured tools and bundles of care have been shown to improve recognition and timely treatment of other obstetrical emergencies, such as postpartum hemorrhage, and have been associated with better outcomes, even in health facilities with limited resources.[22] Moreover, sepsis treatment bundles are widely used in high-income countries, particularly in the nonmaternity population.[23,24] A maternal sepsis treatment bundle has been developed specifically for low-resource settings, but its effect on maternal outcomes has not been established.[25,26]

The Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) program was designed to address these deficiencies through an integrated, multicomponent intervention delivered at the facility level. The program seeks to help health care providers achieve three goals: to improve hand-hygiene adherence, to improve prevention and management of maternal infection, and to increase early recognition and bundled treatment of sepsis.[25,26] We conducted a large cluster-randomized trial in Malawi and Uganda to evaluate whether implementation of the APT-Sepsis program in health facilities would reduce the risk of a composite of infection-related maternal death, infection-related near-miss event, or severe infection-related illness.

METHODS

TRIAL DESIGN AND OVERSIGHT

The APT-Sepsis trial was a multicountry, cluster-randomized trial with a baseline control phase. We designed the intervention to be delivered at the health facility level (cluster) to target the behaviors of health care providers and systems within the facilities.

The trial included a baseline phase for all participating facilities of at least 6 months, during which usual care was provided. On completion of the baseline phase, facilities were randomly assigned in a 1:1 ratio to either continue providing usual care or receive the trial intervention for 12 months. A transition period of 3 months was used to implement and embed the intervention into hospital systems; data from this period were not included in the effectiveness analysis. Participating sites underwent randomization in Malawi from November 6, 2023, to January 8, 2024, and in Uganda from January 8, 2024, to March 4, 2024.

Randomization was performed with the use of a minimization algorithm, generated by an independent statistician, to ensure that the facilities assigned to the intervention and usual-care groups were balanced within each country. Minimization factors were the number of live births per cluster per week (categorized according to small, medium, or large facilities) and the percentage of births with a primary-outcome event (dichotomized with the use of the median value) during the baseline phase. Facilities were assigned sequentially to one of the two trial groups; further details are provided in the Supplementary Appendix, available at NEJM.org. We also conducted a mixed-methods evaluation to explore additional outcomes related to implementation: health care providers' perceptions of acceptability, feasibility of implementation within the health care system, mechanisms of change, and cost (as part of a formal economic evaluation).

The trial was approved by the University of Liverpool, the WHO Ethics Review Committee, the College of Medicine Research Ethics Committee in Malawi, and the Infectious Diseases

Institute Research Ethics Committee and the Uganda National Council for Science and Technology in Uganda. Patients did not provide consent since the intervention was delivered to health care providers, and the components of the intervention were considered best practice. Agreement for participation in the trial was obtained at both the national and facility level.

The trial was overseen by a trial steering committee and an independent data monitoring committee. Patient and public involvement groups provided advice on trial design and materials, how best to engage the public, and trial-related messaging. The first and last authors and the trial statisticians from the Liverpool Clinical Trials Centre vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

PARTICIPATING HOSPITALS

Health facilities in Malawi and Uganda that provided comprehensive obstetrical care (able to perform cesarean births and provide blood transfusions) and had at least 1500 births per year were eligible for inclusion in the trial. Participation was subject to a trial-specific readiness assessment process, which ensured the availability of basic site prerequisites, such as a water supply and electricity. The geographic locations of the facilities were widely spread across both countries.

APT-SEPSIS INTERVENTION AND USUAL CARE

The APT-Sepsis multicomponent intervention was delivered as an integrated program (Fig. 1) that aimed to help health care providers achieve three goals. Goal 1 was adherence to WHO hand-hygiene standards, performed with the correct technique.[19] Goal 2 was the adoption of WHO recommendations on infection prevention and management during and after pregnancy, which includes the evidence-based use of antibiotics for prophylaxis and treatment of common maternal infections, and the correct preparation of the skin and vagina with antiseptic solution before cesarean surgery.[20] Goal 3 was the early detection of sepsis and initiation of the FAST-M (fluids, antibiotics, source identification and control, assessment of the need for transfer to a higher level of care, and monitoring of the woman and baby) treatment bundle when sepsis was suspected. A standardized observation chart that provided clear thresholds for triggering the treatment bundle was used for all the patients in the facilities receiving the intervention. The intervention components were derived with the use of an iterative process of evidence synthesis, international expert consensus, testing, and refinement through multisite pilot studies and mixed-methods evaluation.[25-27]

The implementation strategies in this trial were developed to promote behavior change[28] and included the following key components: hospital leadership engagement, program champions who were selected from existing facility staff, multidisciplinary training with comprehensive training materials, implementation tools (e.g., the FAST-M checklist), and performance feedback provided through dashboards showing local implementation data and at quarterly site visits (Fig. 1); further details are provided in the Supplementary Appendix. In both groups, key resources such as antibiotics were obtained by the facilities through their usual procurement pathways. Additional soap and alcohol-based hand rub were provided to the facilities in the intervention group, if needed. In both groups, a small number of thermometers and blood-pressure machines was also supplied in a single distribution if the equipment at a facility was deemed to be inadequate at the time of the site readiness assessment.

The facilities in the control group continued with usual care and were provided with the relevant WHO and national guidelines on hand hygiene and maternal infection prevention and treatment that informed the APT-Sepsis program (passive guideline dissemination). After the trial ended, the APT-Sepsis program was offered to all the facilities that had been assigned to the usual-care group.

OUTCOME MEASURES

The primary outcome was a composite of infection-related maternal death, infection-related maternal near-miss event (defined as events in which women survived a life-threatening complication), or severe infection-related illness (defined as a deep surgical-site, deep perineal, or body-cavity infection) during pregnancy, childbirth, or within 42 days after pregnancy had ended or at any time up to 28 days after discharge (whichever occurred first), irrespective of birth outcome.

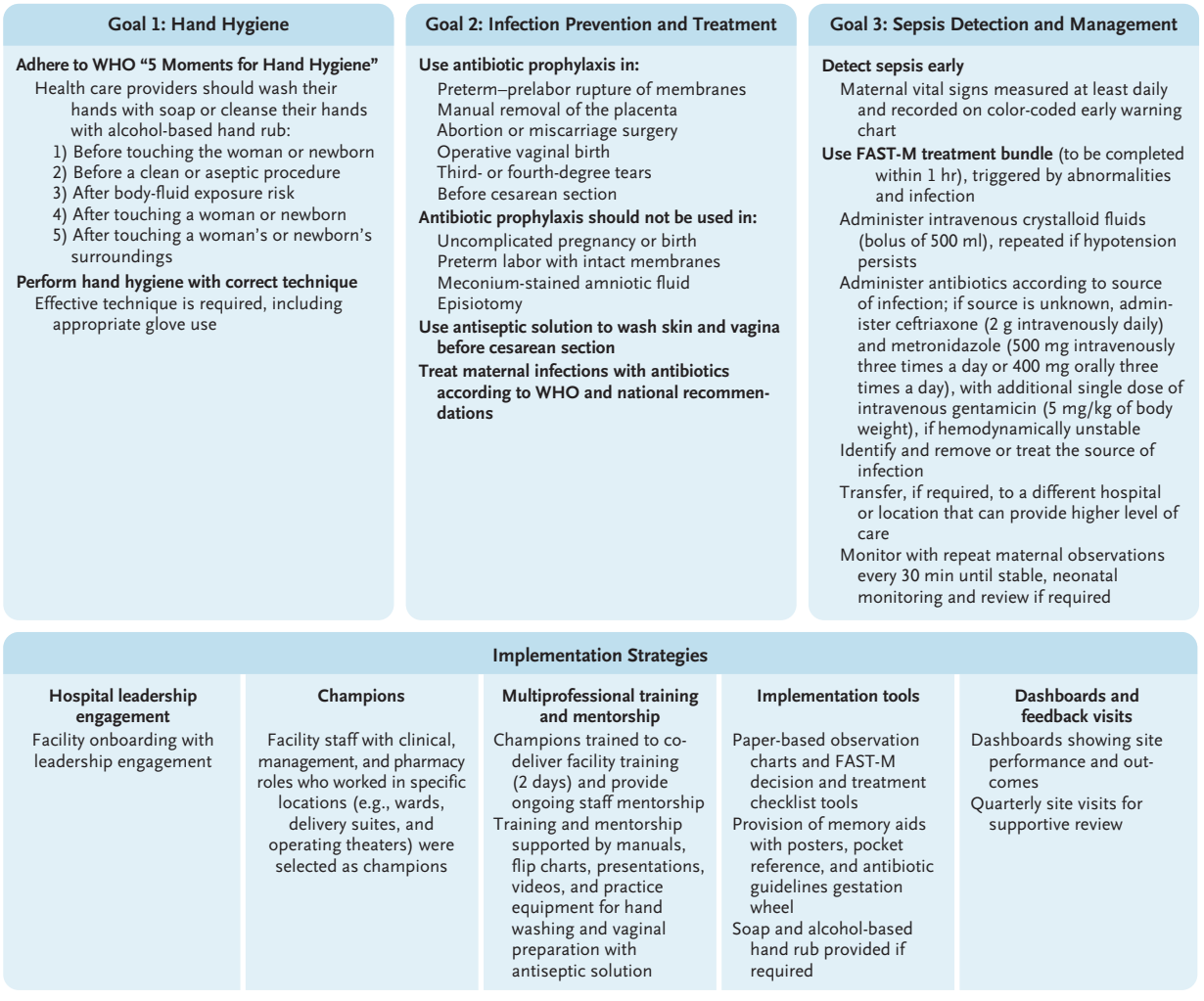

Figure 1. Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) Intervention.

This multicomponent intervention enabled health care providers to meet three goals related to hand hygiene, infection prevention and treatment, and sepsis detection and management, with support from an implementation strategy designed to promote behavioral change. FAST-M denotes fluids, antibiotics, source identification and control, assessment of the need for transfer to a higher level of care, and monitoring of the woman and baby, and WHO World Health Organization.

Detailed definitions of outcomes are provided in the Supplementary Appendix. The WHO criteria for near-miss events were modified to ensure that their ascertainment would not be influenced by the intervention. Modified Centers for Disease Control and Prevention (CDC) criteria were used to define deep surgical-site infection; deep perineal, labial, or vaginal tear infection; and reproductive tract or body-cavity infection within 30 days after the procedure or birth. For maternal death and near-miss events, attribution to maternal infection was assessed on the basis of a review of the full clinical record by the site-based clinical data collector and by the central clinical team in each country. If there was discordance in assessments, or if uncertainty about causation was recorded in either trial group, the case was adjudicated by a separate case classification committee whose members were unaware of the group assignments.

The secondary outcomes included the individual components of the primary composite outcome, stillbirth, neonatal death (infection-related and any cause), maternal death from any cause,

maternal near-miss event from any cause, and maternal severe acute respiratory infection. Clinical outcomes were recorded by the trial staff, independent of the implementation team. Clinical areas were monitored at each site, and objective, structured reporting was conducted daily in the baseline and postrandomization phases. Identification of outcomes involved an active case-finding method, chart review, and assessment of site records.

Additional secondary outcomes related to implementation included adherence to hand hygiene, appropriate use of antibiotic prophylaxis before cesarean section, complete recording of vital signs, and adherence to the maternal sepsis management bundle. These outcomes were measured quarterly during the intervention phase in both groups.

STATISTICAL ANALYSIS

We calculated that at least 60 clusters (a minimum of 30 in Malawi and 30 in Uganda) would provide the trial with 95% power to detect a change in the risk of a primary-outcome event from 3.00% to 2.25% (a 25% relative reduction), at a two-sided P value of less than 0.05. This calculation included adjustment for clustering (with the assumption of an intracluster correlation coefficient of 0.03 [range, 0.001 to 0.05]) and variation in clustering over time (with the assumption of a cluster autocorrelation of 0.97 [range, 0.9 to 1.0]). The original sample size was calculated on the basis of an intervention period of 20 months. A prespecified reestimation of the sample size was performed once the intracluster correlation, baseline event rate, and number of participants per cluster were known from the baseline phase. This analysis showed an intracluster correlation coefficient of 0.02 and a larger than expected number of participants per cluster. On the basis of these findings, shortening the intervention phase was expected to have minimal effect on power, and the independent data monitoring committee and trial steering committee recommended a revised intervention period of 12 months. A full sample-size justification is provided in the trial protocol.

All analyses were performed according to the intention-to-treat principle. No interim analyses were conducted during the trial.

For the primary outcome, we used generalized linear mixed-effects models incorporating a constrained baseline analysis. Both baseline and postrandomization time points were included as outcomes in this analysis, but the treatment effect was constrained to be zero in the baseline phase. We used the binomial distribution and logit link, with robust standard errors, followed by marginal standardization to estimate risk ratios and risk differences. Cluster and cluster by period were included as random effects, with country and the categorical minimization factor of facility size included as covariates. The second minimization factor (percentage of births with a primary-outcome event) was not included because it was already in the model as the outcome variable.

We analyzed the treatment effect on the primary outcome in prespecified subgroups, defined according to country, facility size, and months after implementation. We conducted subgroup analyses by including an interaction parameter between treatment group and subgroup in the regression model and by reporting adjusted treatment effects with 95% confidence intervals.

We analyzed the secondary outcomes with the same methods used for the primary-outcome analysis. Implementation outcomes from the quarterly visits in each facility were analyzed with the use of mixed-effect repeated-measures linear regression, with country and facility size as covariates. There was no prespecified plan to adjust for multiplicity in tests of secondary outcomes. The widths of the 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive effects of the intervention.

RESULTS

HEALTH FACILITY AND PATIENT CHARACTERISTICS

A total of 83 health facilities were identified and assessed for eligibility (Fig. S1 in the Supplementary Appendix). Of these, 33 facilities in Malawi and 38 facilities in Uganda proceeded to initiate the baseline data collection phase and underwent site readiness assessments. Three facilities in Malawi and nine in Uganda were then excluded for one of the following reasons: they did not provide care for patients with severe infections or sepsis within the facility, they no longer met the inclusion criteria, or, in Malawi, the maximum number of facilities had already been enrolled.

A total of 59 facilities underwent randomiza-

tion, with 30 assigned to the intervention group (15 in Malawi and 15 in Uganda) and 29 to the usual-care group (15 and 14, respectively). After randomization, all the facilities followed the trial assignment and completed the trial. A total of 431,394 women had live births during the trial (190,500 in the baseline phase and 240,894 in the intervention phase) (Table 1).

Facility characteristics and resource availability appeared to be generally similar in the intervention group and the usual-care group at baseline; availability was low for some key resources (Table 1). The representativeness of the trial population is summarized in Table S1.

OUTCOMES

During the intervention phase, a primary-outcome event occurred in 1752 of 124,298 women with live births (1.4%) in the intervention group and in 2208 of 116,596 (1.9%) in the usual-care group (risk ratio, 0.68; 95% confidence interval [CI], 0.55 to 0.83; P<0.001) (Table 2, Fig. 2, and Table S2). This finding appeared to be generally consistent between the two countries and across

Table 1. Characteristics of Participating Health Facilities and Resource Availability at Baseline.*

Characteristic	Intervention	Usual Care
No. of live births	94,730	95,770
No. of early pregnancy losses	9,656	9,358
No. of stillbirths	2,267	2,054
Neonatal death — no./total no. (%)	2,334/94,730 (2.5)	2,456/95,770 (2.6)
Vaginal birth — no./total no. (%)	67,343/94,730 (71.1)	70,512/95,770 (73.6)
Forceps or vacuum birth — no./total no. (%)	1,346/94,730 (1.4)	1,564/95,770 (1.6)
Cesarean section birth — no./total no. (%)	24,154/94,730 (25.5)	21,205/95,770 (22.1)
Vaginal breech delivery birth — no./total no. (%)	1,346/94,730 (1.4)	1,564/95,770 (1.6)
Born before arrival — no./total no. (%)	1,259/94,730 (1.3)	1,575/95,770 (1.6)
Postpartum hemorrhage (>1 liter) — no./total no. (%)	1,680/94,730 (1.8)	1,355/95,770 (1.4)
Severe preeclampsia or eclampsia — no./total no. (%)	1,201/94,730 (1.3)	1,262/95,770 (1.3)
Median availability of key resources (IQR) — % of weeks available†		
Functioning autoclave	100 (97.1–100)	100 (96.0–100)
Running water	83.7 (8.8–97.1)	85.4 (35.3–96.9)
Thermometers	44.4 (4.0–80.5)	19.5 (5.6–71.9)
Blood-pressure devices	6.8 (0–16.7)	2.6 (0–19.5)
Soap	80.9 (43.8–96.9)	71.9 (38.2–94.1)
Alcohol-based hand rub	66.1 (31.7–88.9)	68.8 (36.1–92.7)
Oxygen concentrators	54.6 (7.3–83.3)	44.4 (2.6–84.4)
Bottle or piped oxygen	9.9 (0–46.9)	0 (0–25.0)
Intravenous crystalloid fluid	84.7 (61.0–95.1)	81.6 (50.0–96.9)
Intravenous cephalosporin	66.6 (33.3–92.7)	75.6 (58.8–87.5)
Intravenous metronidazole	60.6 (36.6–82.4)	63.2 (44.1–81.3)
Intravenous gentamicin	72.1 (50.0–82.9)	65.9 (55.6–93.8)

* A total of 59 facilities underwent randomization, with 30 assigned to the intervention group and 29 to the usual-care group. Health facilities in the intervention phase implemented the APT-Sepsis intervention. This was a cluster-randomized trial with a baseline phase. The characteristics reported here are from the baseline phase, before randomization.
† Availability of key resources was recorded weekly from key clinical areas as either available, limited, or not available in each facility. Shown is the median percentage of weeks for which the resource was available in all areas assessed.

small, medium, and large facilities. The percentage of patients in the intervention group with a primary-outcome event progressively decreased after randomization, from a mean of 2.4% in the baseline phase, 2.0% in the first month after completion of the transition phase, and 0.9% in the final month of the trial (Fig. 3 and Table S4). There appeared to be a corresponding increase

Table 2. Primary and Secondary Outcomes.*

Outcome	Intervention (N=124,298)	Usual Care (N=116,596)	Risk Ratio or Mean Difference (95% CI)†
Primary outcome			
Composite of infection-related maternal death; infection-related near-miss event; or severe infection-related illness — no. (%)‡	1752 (1.4)	2208 (1.9)	0.68 (0.55 to 0.83)
Components of the primary outcome§			
Infection-related maternal death — no. (%)	90 (0.1)	77 (0.1)	0.96 (0.69 to 1.32)
Infection-related near-miss event — no. (%)	119 (0.1)	141 (0.1)	0.82 (0.54 to 1.25)
Deep surgical-site, deep perineal, or body-cavity infection — no. (%)	1672 (1.3)	2102 (1.8)	0.68 (0.55 to 0.84)
Secondary outcomes			
Stillbirth — no./total no. (%)¶	2708/127,006 (2.1)	2314/118,910 (1.9)	0.90 (0.73 to 1.10)
Neonatal death — no. (%)‖	2691 (2.2)	2761 (2.4)	0.88 (0.73 to 1.04)
Neonatal death (infection-related) — no. (%)	819 (0.7)	622 (0.5)	0.86 (0.57 to 1.30)
Maternal death (any cause) — no. (%)	288 (0.2)	235 (0.2)	0.96 (0.74 to 1.24)
Maternal near-miss event (any cause) — no. (%)	771 (0.6)	609 (0.5)	0.90 (0.73 to 1.10)
Maternal severe acute respiratory infection — no. (%)**	10 (<0.1)	7 (<0.1)	1.04 (0.45 to 2.39)
Implementation outcomes††			
Adherence to hand hygiene — %	32.9±19.3	15.1±10.5	14.48 (10.1 to 18.9)
Appropriate cesarean section antibiotic prophylaxis — %	73.7±32.5	57.7±36.4	15.0 (4.0 to 26.0)
Complete vital signs recorded at admission — %	48±29	14.5±19.5	32.4 (24.5 to 40.4)
Patients with suspected sepsis with complete vital signs recorded — %	59.9±32.6	33.9±39.0	27.7 (15.2 to 40.2)
Patients with suspected sepsis given intravenous fluids within 1 hr — %	32.9±33.6	21.9±24.5	13.4 (4.8 to 22.0)
Patients with suspected sepsis given antibiotics within 1 hr — %	43.6±37.5	38.4±37.7	8.2 (−2.7 to 19.0)

* Plus–minus values are means ±SD.

† Risk ratios are reported for the primary outcome, the components of the primary outcome, and the secondary outcomes. Risk ratios were estimated by fitting a mixed-effects logistic regression model, incorporating a constrained baseline analysis, followed by marginal standardization. Mean differences are reported for the implementation outcomes. The width of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used to infer treatment effects.

‡ The primary outcome was a composite of infection-related maternal death, infection-related maternal near-miss event (defined according to adapted World Health Organization criteria as events in which women survived a life-threatening complication), or severe infection-related illness (deep surgical-site, deep perineal, or body-cavity infection; defined according to the adapted Centers for Disease Control and Prevention definition of deep surgical-site infection or body-cavity infection) during pregnancy, childbirth, or within 42 days of pregnancy ending or at any time up to 28 days of discharge (whichever occurred first). The denominator is live births. The intracluster correlation coefficient for the primary outcome was 0.004 (95% CI, 0.003 to 0.005). The cluster autocorrelation for the primary outcome was 0.398. The intracluster correlation coefficient and cluster autocorrection were estimated by fitting a mixed-effects linear model to the data with random effects for cluster and for a cluster–period interaction. P<0.001 for the comparison of the intervention with usual care.

§ A patient could be included in more than one component of the primary outcome but would only have been counted once when the primary outcome was calculated.

¶ Stillbirth was defined as any death before or during birth after a gestational age of 28 weeks, with gestational age determined by the facility medical team. The denominator includes live-born and stillborn infants.

‖ Neonatal death was defined as death of a live-born infant within the first 28 completed days of life; only deaths that occurred within the health facility were reported.

** Maternal severe acute respiratory infection was defined as a death or near-miss event owing to maternal severe acute respiratory infection.

†† Implementation outcomes were measured during quarterly site assessment visits, and are reported as a mean proportion of opportunities or cases in which there was adherence. The unit of analysis was the facility-quarter rather than the patient. Mean differences and 95% confidence intervals are compared between the intervention and usual-care groups.

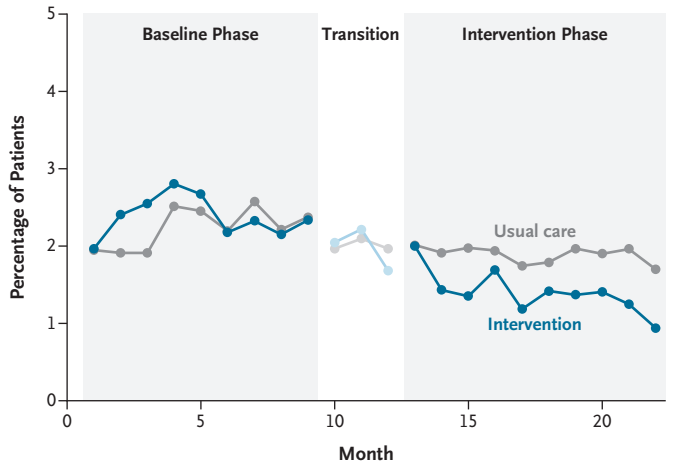

Figure 2. Patients with Primary-Outcome Event during the Baseline, Transition, and Intervention Phases.

The primary outcome was a composite of infection-related maternal death, infection-related maternal near-miss event (events in which women survived a life-threatening complication, according to adapted World Health Organization criteria), or severe infection-related illness (defined as deep surgical-site, perineal, or body-cavity infection; adapted from Centers for Disease Control and Prevention definition of deep surgical-site infection or body-cavity infection) during pregnancy, childbirth, or within 42 days of pregnancy ending or at any time up to 28 days of discharge (whichever occurred first).

in the size of the effect that was observed from the first month (risk ratio, 0.92; 95% CI, 0.68 to 1.25) to the final month (risk ratio, 0.53; 95% CI, 0.35 to 0.80) of the intervention phase (Fig. 3).

The results for the individual components of the primary outcome are shown in Table 2. The reduction in the risk of the composite primary outcome appeared to be largely driven by the incidence of severe infection-related illness, which occurred in 1.3% of the patients in the intervention group and in 1.8% of those in the usual-care group (risk ratio, 0.68; 95% CI, 0.55 to 0.84).

Stillbirths were recorded in 2.1% of the total births in the intervention group and in 1.9% of those in the usual-care group (risk ratio, 0.90; 95% CI, 0.73 to 1.10). Neonatal deaths were recorded in 2.2% of the infants in the intervention group and in 2.4% of those in the usual-care group (risk ratio, 0.88; 95% CI, 0.73 to 1.04); the percentage of deaths that were determined to be related to infection was 0.7% and 0.5%, respectively (risk ratio, 0.86; 95% CI, 0.57 to 1.30) (Table 2).

The intervention was associated with improvements in the prespecified implementation outcomes associated with the three goals of the trial, which were measured during quarterly assessment visits (Table 2). The mean adherence to hand-hygiene standards (goal 1) was 33% in the intervention group and 15% in the usual-care group (mean difference, 14%; 95% CI, 10 to 19). Appropriate antibiotic prophylaxis was administered before cesarean section (goal 2) in 74% of the cases in the intervention group and in 58% of those in the usual-care groups, respectively (mean difference, 15%; 95% CI, 4 to 26). Several measures related to goal 3 also supported the results for the primary outcome; for example, complete vital signs were recorded at admission in 48% of the patients in the intervention group and in 15% of the patients in the usual-care group (mean difference, 32%; 95% CI, 25 to 40), and among patients with suspected sepsis, antibiotics were administered within 1 hour in 44% and 38% of the patients in the intervention and usual-care groups, respectively (mean difference 8%; 95% CI, −3 to 19).

DISCUSSION

In this cluster randomized trial, implementation of the APT-Sepsis program significantly lowered the risk of a composite of infection-related maternal death, infection-related near-miss event, or severe infection-related illness than usual care among women who were pregnant or had recently been pregnant. This benefit was driven by the reduction in the risk of deep surgical-site, perineal, or body-cavity infection with the intervention, was consistent across countries and facility size, and was sustained throughout the trial.

The scale of the trial, which included government and nongovernment facilities of different sizes, supports the generalizability of the findings to health facilities that provide comprehensive obstetrical care. The intervention also covered the continuum of pregnancy-related infections, including those that occur in early pregnancy or after an induced or spontaneous abortion. The intervention involved the provision of relatively few additional resources beyond what was generally available within the hospital systems, which suggests feasibility beyond the trial setting. For example, minimal equipment was provided, and site champions were not paid for this extra role.

The results for the implementation outcomes

Subgroup	Intervention	Usual Care	Risk Ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
Country			
Malawi	626/63,363 (1.0)	986/70,615 (1.4)	0.68 (0.53–0.87)
Uganda	1126/60,935 (1.8)	1222/45,981 (2.7)	0.68 (0.52–0.90)
Facility size			
Small	335/22,102 (1.5)	507/24,304 (2.1)	0.63 (0.48–0.82)
Medium	553/39,284 (1.4)	644/30,323 (2.1)	0.70 (0.52–0.94)
Large	864/62,912 (1.4)	1057/62,239 (1.7)	0.71 (0.49–1.02)
Time point after randomization			
Month 1	254/12,703 (2.0)	244/12,118 (2.0)	0.92 (0.68–1.25)
Month 2	176/12,295 (1.4)	230/12,009 (1.9)	0.67 (0.51–0.88)
Month 3	174/12,872 (1.4)	240/12,136 (2.0)	0.63 (0.46–0.86)
Month 4	209/12,363 (1.7)	227/11,682 (1.9)	0.78 (0.57–1.06)
Month 5	150/12,664 (1.2)	204/11,696 (1.7)	0.60 (0.41–0.88)
Month 6	185/13,026 (1.4)	220/12,285 (1.8)	0.70 (0.49–1.00)
Month 7	170/12,415 (1.4)	226/11,478 (2.0)	0.64 (0.45–0.92)
Month 8	178/12,646 (1.4)	225/11,842 (1.9)	0.68 (0.49–0.94)
Month 9	148/11,848 (1.2)	218/11,116 (2.0)	0.60 (0.44–0.82)
Month 10	108/11,466 (0.9)	174/10,235 (1.7)	0.53 (0.35–0.80)

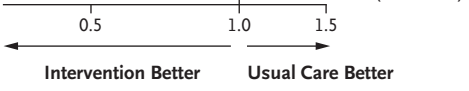

Figure 3. Prespecified Subgroup Analyses of the Primary Outcome.

The forest plot shows the primary outcome (a composite of infection-related maternal death, infection-related maternal near-miss event, or severe infection-related illness, assessed among women who were pregnant or had recently been pregnant) in prespecified subgroups based on country, facility size (defined according to small, medium, or large facilities within each country at the point of randomization), and time point after randomization (in months). The size of each square is proportional to the number of patients in each subgroup. The I bars indicate 95% confidence intervals. The widths of the confidence intervals for these analyses have not been adjusted for multiplicity and should not be used to infer definitive effects of the intervention.

indicated improvement in the intervention group with respect to all three program goals. However, adherence was incomplete; this was not unexpected given that the program did not address broader health system challenges (e.g., staffing shortages, inadequate sinks for hand washing, and limited availability of antibiotics). The observed clinical benefit despite modest changes in some implementation measures may be a result of the simultaneous targeting of multiple points in the pathway to maternal sepsis and adverse outcomes.

A recent trial showed that the use of azithromycin prophylaxis before all vaginal births reduced the risk of maternal sepsis,[29] but this practice has not been routinely implemented owing to concerns regarding antimicrobial resistance.[30] The intervention used in this trial reduced the risk of maternal infection through targeted use of antibiotics together with nonpharmacologic changes in care.

This trial has several limitations. The multicomponent nature of the intervention precludes attribution of the effect to individual elements. Microbiologic data were not available, so pathogen-specific diagnoses and resistance profiling were not possible. Since the trial staff who identified the outcomes were aware of the group assignments, and because there is subjectivity in identifying the relatedness of the outcomes to infection, bias is possible. However, clinical outcomes were identified with the use of objective criteria, and data were obtained daily by trained staff who were not involved in implementation. Identification of outcomes after hospital discharge required that the patient return for care, so underreporting is possible but unlikely given the serious nature of these outcomes. Extending this intervention to other countries and settings may require partnering with national ministries of health, as in this trial, to facilitate uptake of the intervention and to adapt materials and processes to ensure they are culturally and contextually appropriate. Further work is needed to

evaluate patient and provider experiences, behavior changes, and the cost-effectiveness of the intervention.

Implementation of the APT-sepsis program led to a significantly lower risk of a composite outcome of infection-related maternal death, infection-related near-miss event, or severe infection-related illness than usual care.

The views and opinions in this article are those of the authors and do not necessarily reflect those the National Institute of Health Research (NIHR), U.K. National Health Service, or the U.K. Department of Health and Social Care.

Supported by a grant (MRV005782/1) from the Joint Global Health Trials scheme, which included the U.K. Foreign, Commonwealth, and Development Office, the U.K. Medical Research Council, the U.K. Department of Health and Social Care through the NIHR, and Wellcome; the Human Reproduction Program (UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development, and Research Training in Human Reproduction); and funding from the NIHR (to David Lissauer, as the NIHR Global Health Research Professor in Maternal and Fetal Health). The FAST-M (fluids, antibiotics, source identification and control, assessment of the need for transfer to a higher level of care, and monitoring of the woman and baby) treatment bundle was developed with support from Merck (known outside the United States as Merck Sharpe and Dohme [MSD]), through the MSD for Mothers program, an initiative of Merck.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

David Lissauer, Ph.D.,[1,2] Luis Gadama, M.Med.,[3] Catriona Waitt, Ph.D.,[1,4] Sonia Whyte, M.Sc.,[1] Girvan Burnside, Ph.D.,[5,6] Aiswarya Anilkumar, M.Sc.,[6] Regina Makuluni, M.Sc.,[2] Peace Okwaro, B.Sc.,[4] Liu Yang, Ph.D.,[7] Peter Waitt, M.B., Ch.B.,[1,4,8] Owen Musopole, M.Sc.,[9] Rosemary Bilesi, M.Sc.,[9] Bertha Maseko, M.Sc.,[2] Joel Lwasa, M.Med.,[10] Richard Mugahi, M.Sc.,[11] Charles Olaro, M.Med.,[11] Mohammed Lamorde, Ph.D.,[12] Mirriam Makuta, B.Sc.,[2] Chimwemwe Kachiwaya, B.Sc.,[2] Tionge Mkandawire, B.Sc.,[2] Adrian Malunga, B.Sc.,[2] Nyadani Chitsulo, B.Sc.,[2] Prisca Abitimo, Dip. Midwifery,[4] Tabitha Ayabo, B.Sc.,[4] Andrew Weeks, M.D.,[1] James Martin, Ph.D.,[13] Karla Hemming, Ph.D.,[13] Ioannis Gallos, M.D.,[14] Edward J. M. Monk, M.Sc.,[15] Jennifer Riches, M.B., Ch.B.,[1] Chikondi Chapuma, M.P.H.,[2] Judith Nanyondo S., M.P.H.,[16] Fabiana Lorencatto, Ph.D.,[17] Mark Monahan, Ph.D.,[18] Benedetta Allegranzi, M.D.,[19] Catherine Dunlop, Ph.D.,[20] Lou Atkins, Ph.D.,[17] Anna Rosala-Hallas, M.Sc.,[6] Tracy Roberts, Ph.D.,[18] Carrol Gamble, Ph.D.,[6] Address Malata, Ph.D.,[21] Nicola Desmond, Ph.D.,[15] Edward Kommwa, M.Med.,[22] Abi Merriel, Ph.D.,[1] William Parry-Smith, M.D.,[23,24] Rebecca Smith, M.B., Ch.B.,[1] Ivy Ndumu, M.Sc.,[18] Eleanor Williams, M.Sc.,[18] Bob Faque, M.Sc.,[2] Gertrude Banda, M.Sc.,[2] Alinane L. Nyondo-Mipando, Ph.D.,[1] Adelline Twimukye, M.A.,[4] Tim Chater, B.Sc.,[6] Aristotelis Diplas, M.Sc.,[6] Vanessa Brizuela, Dr.PH.,[14] Joao Paulo Souza, M.D., Ph.D.,[25,26] Jamie Rylance, Ph.D.,[27] James Cheshire, Ph.D.,[20] Lydia Hawker, M.B., Ch.B.,[1] Arri Coomarasamy, Ph.D.,[28] and Mercedes Bonet, Ph.D.[14]

[1] Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool Women's Hospital, Liverpool, United Kingdom; [2] Malawi Liverpool Wellcome Research Program, Blantyre, Malawi; [3] Kamuzu University of Health Sciences, Blantyre, Malawi; [4] Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda; [5] Institute of Population Health, University of Liverpool, Liverpool, United Kingdom; [6] Liverpool Clinical Trials Centre, University of Liverpool, Liverpool, United Kingdom; [7] Great Ormond Street Institute of Child Health, University College London, London; [8] Wirral University Teaching Hospital NHS Foundation Trust, Upton, United Kingdom; [9] Malawi Ministry of Health, Lilongwe, Malawi; [10] Kawempe National Referral Hospital, Kampala, Uganda; [11] Ministry of Health, Kampala, Uganda; [12] Resolve to Save Lives, Abuja, Nigeria; [13] Department of Applied Health Sciences, University of Birmingham, Birmingham, United Kingdom; [14] UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development, and Research Training in Human Reproduction (Human Reproduction Program), Department of Sexual, Reproductive, Maternal, Child, Adolescent Health, and Ageing, World Health Organization, Geneva; [15] London School of Hygiene and Tropical Medicine, London; [16] Palladium, Kampala, Uganda; [17] Centre for Behaviour Change, University College London, London; [18] Department of Applied Health Sciences, University of Birmingham, Birmingham, United Kingdom; [19] World Health Organization, Eastern Mediterranean Regional Office, Cairo; [20] Department of Metabolism and Systems Sciences, University of Birmingham, Birmingham, United Kingdom; [21] Malawi University of Science and Technology, Limbe, Malawi; [22] Partners in Health–Sierra Leone, Freetown; [23] Keele University, School of Medicine, Keele, United Kingdom; [24] Telford Hospitals NHS Trust, Princess Royal Hospital, Apley Castle, Telford, United Kingdom; [25] Department of Social Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [26] Pan American Health Organization, Americas Regional Office, World Health Organization, Washington, DC; [27] World Health Emergencies Program, World Health Organization, Geneva; [28] Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom.

REFERENCES

1. Cresswell JA, Alexander M, Chong MYC, et al. Global and regional causes of maternal deaths 2009-20: a WHO systematic analysis. Lancet Glob Health 2025; 13(4):e626-e634.

2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.

3. Bonet M, Brizuela V, Abalos E, et al. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. Lancet Glob Health 2020;8(5):e661-e671.

4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858.

5. Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection: a systematic review and meta-analysis. PLoS Med 2019;16(12):e1002984.

6. Firoz T, Trigo Romero CL, Leung C, Souza JP, Tunçalp Ö. Global and regional estimates of maternal near miss: a systematic review, meta-analysis and experiences with application. BMJ Glob Health 2022;7(4):e007077.

7. Baguiya A, Bonet M, Cecatti JG, et al. Perinatal outcomes among births to women with infection during pregnancy. Arch Dis Child 2021;106:946-53.

8. Vogel JP, Souza JP, Mori R, et al. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal

and Newborn Health. BJOG 2014;121: Suppl 1:76-88.
9. Statement on maternal sepsis. Geneva: World Health Organization, 2017 (https://www.who.int/publications/i/item/WHO-RHR-17.02).
10. Global Maternal and Neonatal Sepsis Initiative Working Group. The Global Maternal and Neonatal Sepsis Initiative: a call for collaboration and action by 2030. Lancet Glob Health 2017;5(4):e390-e391.
11. 2030 Global agenda for sepsis. Berlin: Global Sepsis Alliance, 2024. (https://static1.squarespace.com/static/58a7025b8419c215b30b2df3/t/67d1879b8dbfb06f8c3be697/1741784989573/2030_Global_Agenda_for_Sepsis_Online.pdf).
12. World Health Assembly. Improving the prevention, diagnosis, and clinical management of sepsis. Geneva: World Health Organization, 2017 (https://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R7-en.pdf).
13. World Health Assembly. Accelerate progress towards reducing maternal, newborn, and child mortality in order to achieve Sustainable Development Goal targets 3.1 and 3.2. Geneva: World Health Organization, 2024 (https://apps.who.int/gb/ebwha/pdf_files/WHA77/A77_ACONF5-en.pdf).
14. Gon G, de Barra M, Dansero L, Nash S, Campbell OMR. Birth attendants' hand hygiene compliance in healthcare facilities in low and middle-income countries: a systematic review. BMC Health Serv Res 2020;20:1116.
15. Kodan LR, Verschueren KJC, Kanhai HHH, van Roosmalen JJM, Bloemenkamp KWM, Rijken MJ. The golden hour of sepsis: an in-depth analysis of sepsis-related maternal mortality in middle-income country Suriname. PLoS One 2018;13(7):e0200281.
16. Cebekhulu S, Cornelissen L, Pattinson R. Too little, too late: the recurrent theme in maternal deaths due to sepsis. Obstet Gynaecol Forum 2018;28:9-12 (https://hdl.handle.net/10520/EJC-11ea4f673a).
17. Brizuela V, Cuesta C, Bartolelli G, et al. Availability of facility resources and services and infection-related maternal outcomes in the WHO Global Maternal Sepsis Study: a cross-sectional study. Lancet Glob Health 2021;9(9):e1252-e1261.
18. Abdu M, Wilson A, Mhango C, Taki F, Coomarasamy A, Lissauer D. Resource availability for the management of maternal sepsis in Malawi, other low-income countries, and lower-middle-income countries. Int J Gynaecol Obstet 2018;140:175-83.
19. WHO guidelines on hand hygiene in health care. Geneva: World Health Organization, 2009 (https://iris.who.int/handle/10665/44102).
20. WHO recommendations for the prevention and treatment of maternal peripartum infections. Geneva: World Health Organization, 2015 (https://iris.who.int/handle/10665/186171).
21. Abortion care guideline. 2nd ed. Geneva: World Health Organization, 2024 (https://iris.who.int/handle/10665/382157).
22. Gallos I, Devall A, Martin J, et al. Randomized trial of early detection and treatment of postpartum hemorrhage. N Engl J Med 2023;389:11-21.
23. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
24. Lissauer D, Morgan M, Banerjee A, Plaat F, Pasupathy D, Royal College of Obstetrics and Gynaecology. Identification and management of maternal sepsis during and following pregnancy. BJOG 2025;132(4):e61-e85.
25. Cheshire J, Jones L, Munthali L, et al. The FAST-M complex intervention for the detection and management of maternal sepsis in low-resource settings: a multisite evaluation. BJOG 2021;128:1324-33.
26. Lissauer D, Cheshire J, Dunlop C, et al. Development of the FAST-M maternal sepsis bundle for use in low-resource settings: a modified Delphi process. BJOG 2020;127:416-23.
27. Dunlop CL, Kilpatrick C, Jones L, et al. Adapting the WHO hand hygiene 'reminders in the workplace' to improve acceptability for healthcare workers in maternity settings worldwide: a mixed methods study. BMJ Open 2024;14(9):e083132.
28. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42.
29. Tita ATN, Carlo WA, McClure EM, et al. Azithromycin to prevent sepsis or death in women planning a vaginal birth. N Engl J Med 2023;388:1161-70.
30. WHO recommendation on antibiotic prophylaxis during labour for vaginal birth. Geneva: World Health Organization, 2025 (https://www.who.int/publications/i/item/9789240115750).