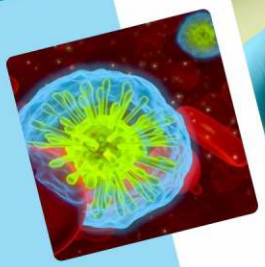
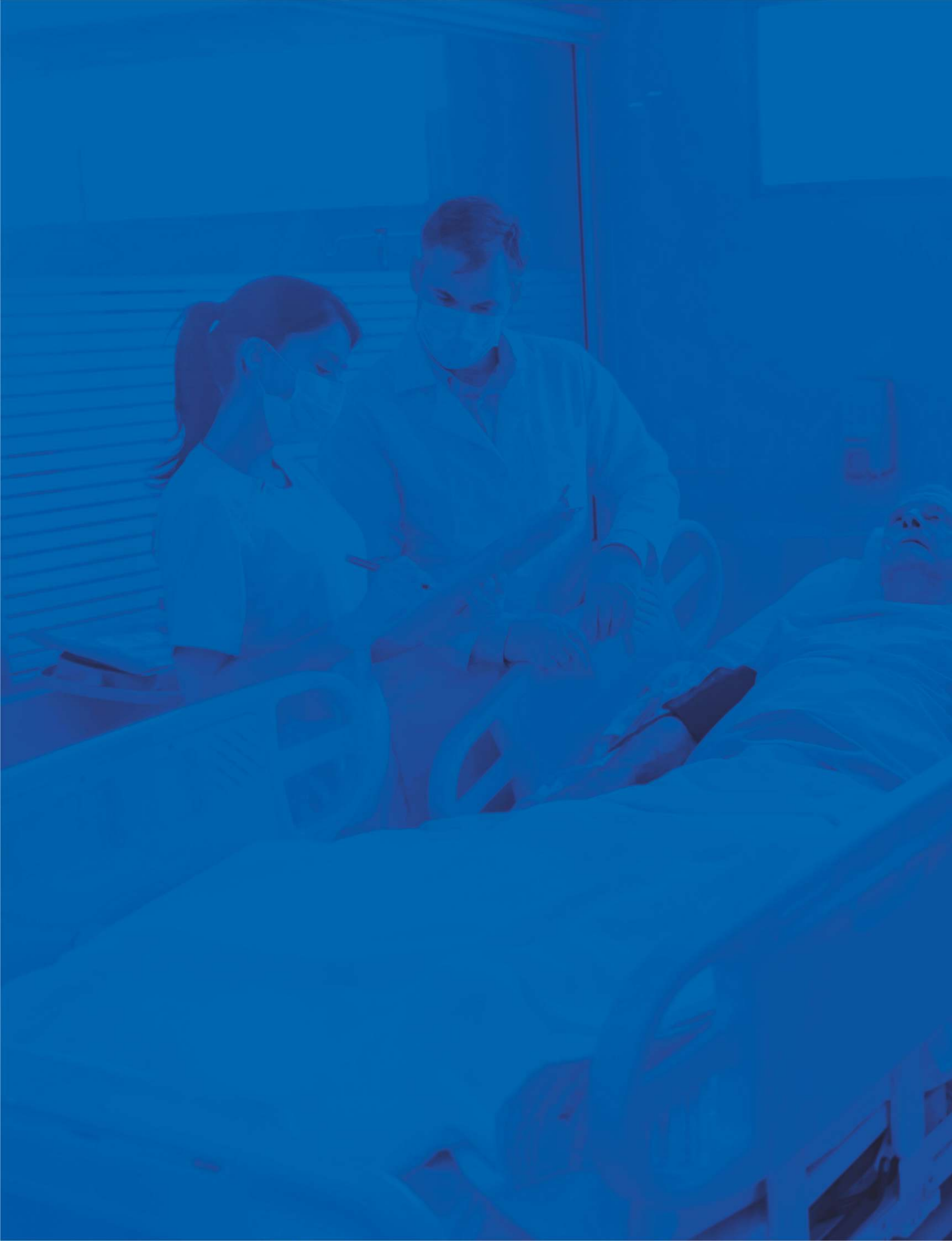


# Sepsivac™

(Heat killed Mw)

## Save More Lives

COMPENDIUM



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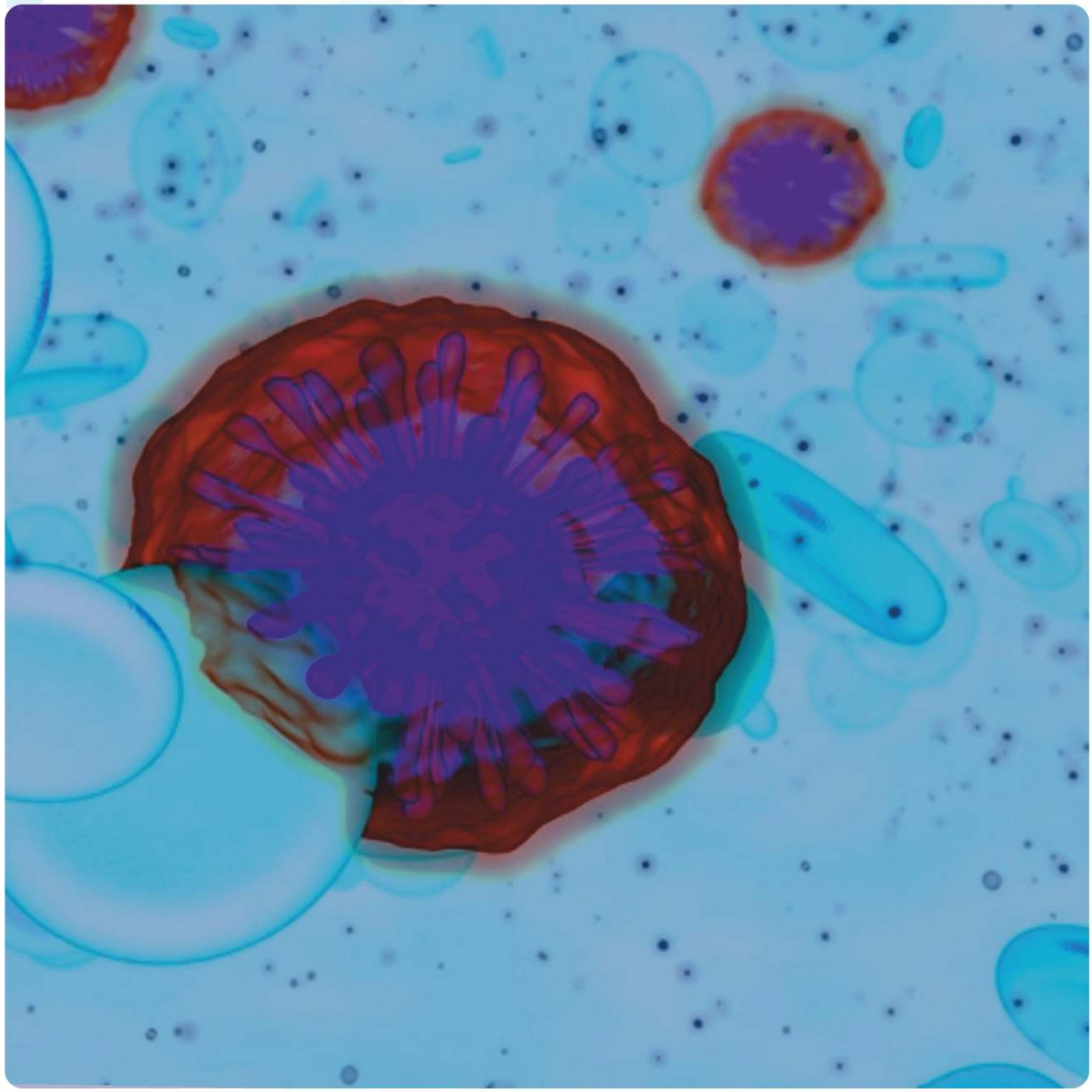


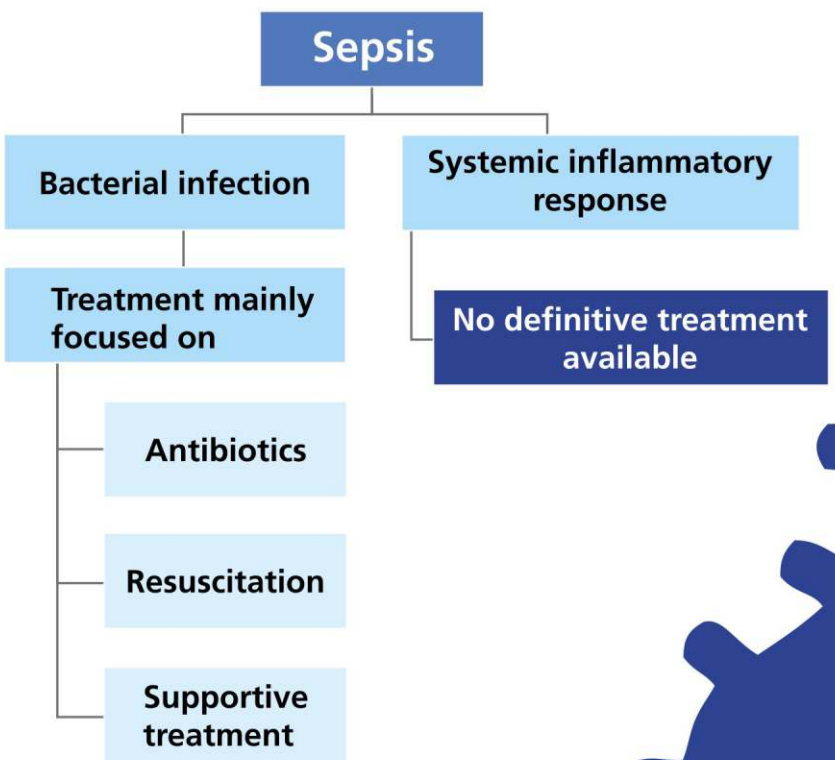
# There is a potential therapy gap for the treatment of the inflammatory component of sepsis

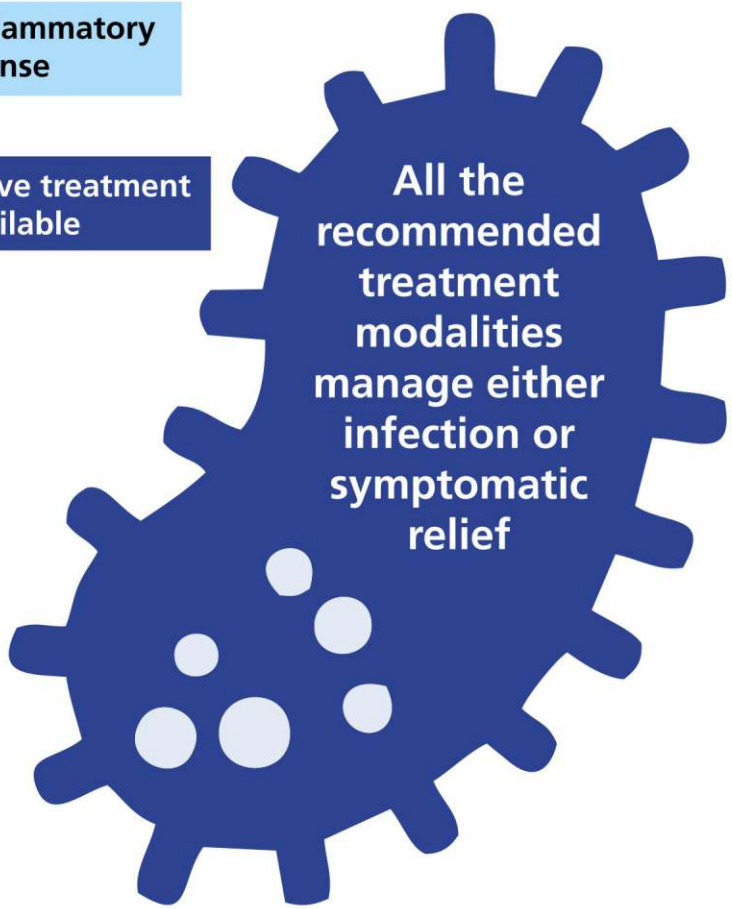
# SEPSIS

**Life-threatening organ dysfunction** caused by a dysregulated host response to infection[1]

It Accounts for **6% to 30%** of all intensive care unit **(ICU) admissions**[2,3]

In India **prevalence** of severe sepsis is **28.3% out of which 20.5%** are ICU acquired [4,5]



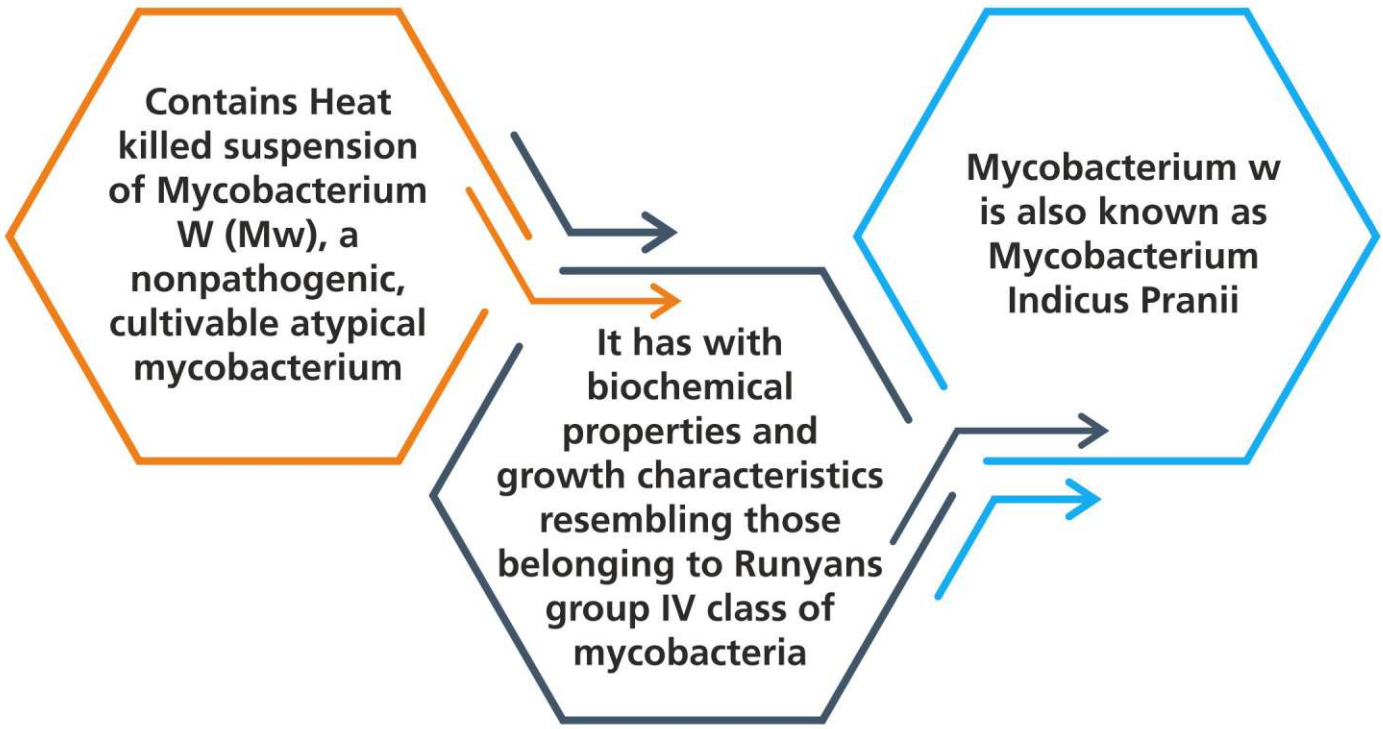

Ref.: **1.** Curr Opin Anesthesiol 2017, 30:200–204,
**2.** Expert Rev Anti Infect Ther 2012;10(6):701–6,
**3.** Crit Care Med 2013;41(10):2458–60.
**4.** Indian J Crit Care Med. 2017 Sep; 21(9): 573–577,
**5.** Indian J Crit Care Med. 2016 Apr; 20(4): 216–225
**6.** Intensive Care Med. 2017 Mar;43(3):304-377

*Introducing*

# Sepsivac™

(Heat killed Mw)

## Save More Lives




### Mode of administration

0.3 ml drug is to be injected

**Intradermally**

At different sites (0.1 ml each site)

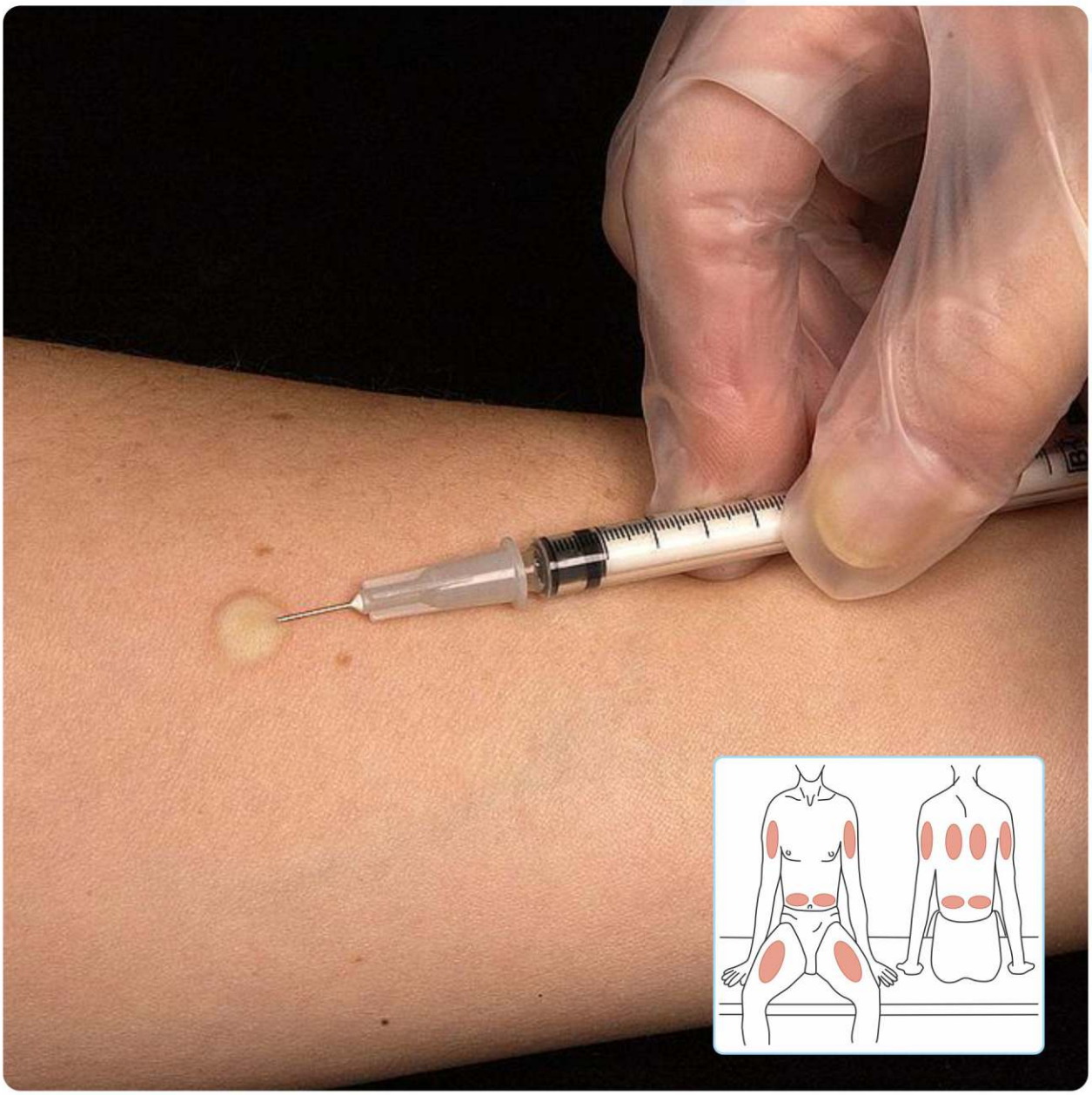
For 3 consecutive days

Microbes and Infection 14 (2012) 348e356

### Modes of action of Sepsivac

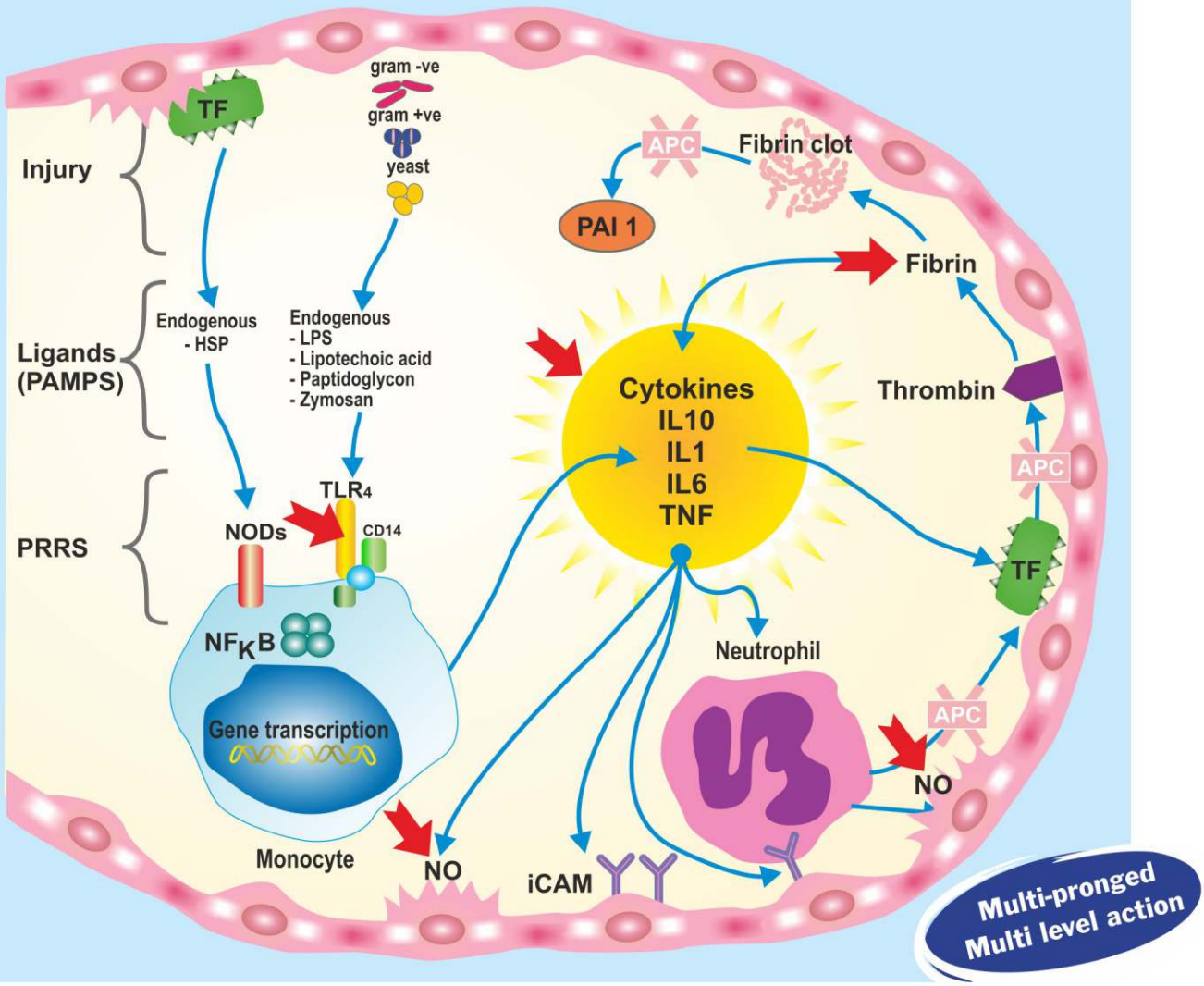
- Poly TLR antagonist (TLR – 4, 5, 7, 9)
- MAPK modulator
- Cytokine suppressor
- Inhibitor of cytokine - induced NO release
- Reverser of LPS induced events (Mediated by TLR 4 Antagonism)

TLR: Toll like receptor, MAPK: Mitogen-activated protein kinases, NO: nitrous oxide, LPS: Lipopolysaccharide



## It is a known immunomodulator

# Mechanism of action

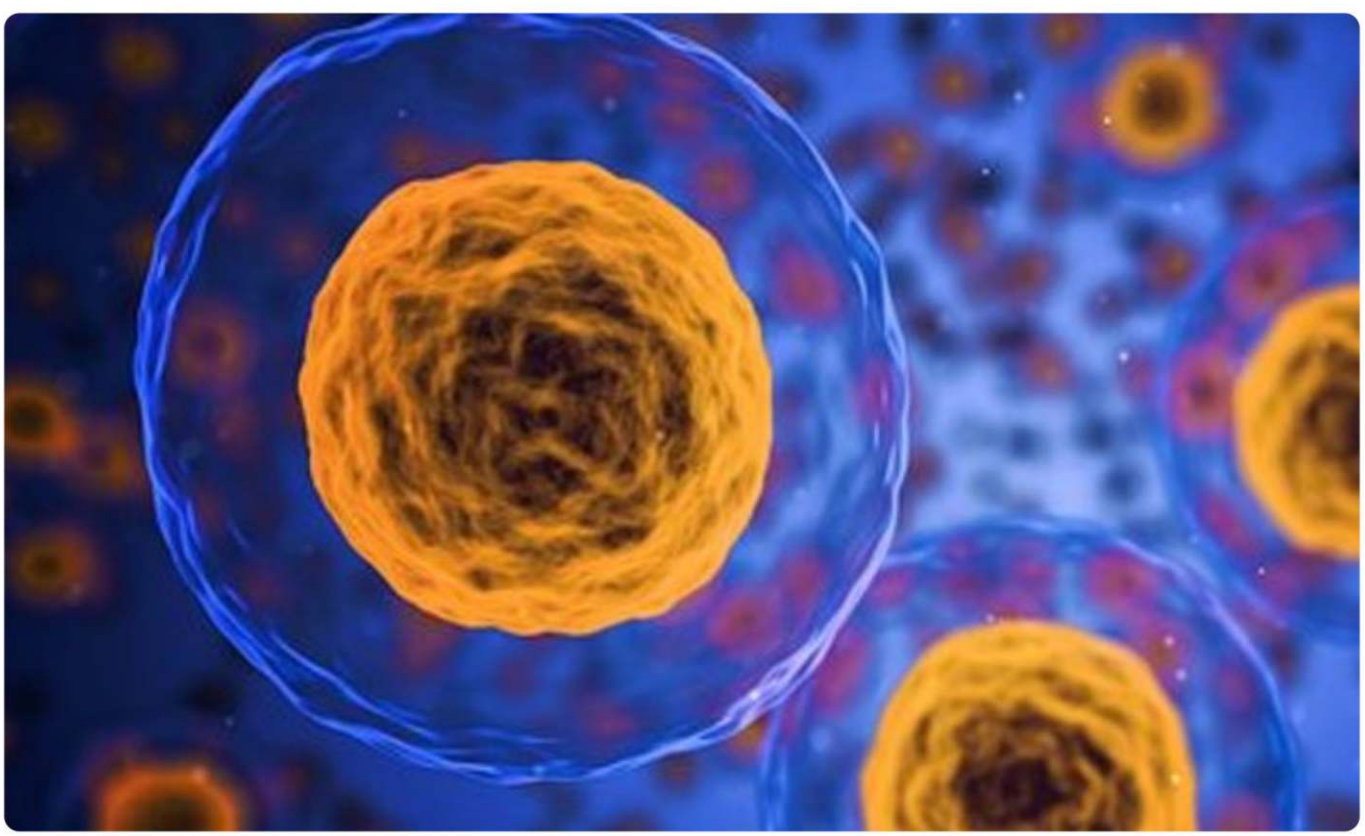



**Sepsivac blocks TLR4, production of various cytokines, NO as well as fibrin**

(TLR4: Toll Like Receptor 4, NO: Nitric Oxide, IL: Interleukin, APC: Activated Protein C, TNF: Tumour Necrosis Factor)

## In a gene expression study, Sepsivac was found to reverse the changes induced by sepsis. Some of the important genes are:

| Gene | Sepsivac* | Sepsis | Remark |
|---|---|---|---|
| IL - 1b | ↓ | ↑ | Proinflammatory cytokine |
| IL - 6r | ↓ | ↑ | Proinflammatory cytokine |
| TNF - alpha induced protein 6 | ↓ | ↑ | Increased levels in non survivors |
| HMGB - 1 and 2 | ↓ | ↑ | Mediator of lethal sepsis |
| VEGF - d | ↓ | ↑ | Promotes homeostasis during sepsis. |
| TIMP - 1 | ↓ | ↑ | Metallo - protease - tissue damage |
| Phospholipase A2, group 1 B | ↓ | ↑ | Involved in production of inflammatory mediators |



# Clinical evidences – Phase IIb

**Randomized, double blind, two arm, comparative controlled, prospective clinical trial of Sepsivac in combination with standard therapy vs standard therapy alone in sepsis due to gram –ve infection**

**Phase IIb study**

**Patients with severe Sepsis due to Gram Negative Infection**

**Screening**

**Randomization (Day 1)**

**Test Drug: 0.3ml (0.1ml x 3 Inj.) daily for 3 days (N=101)**

**Placebo Drug: 0.3ml (0.1ml x 3 Inj.) daily for 3 days (N=101)**

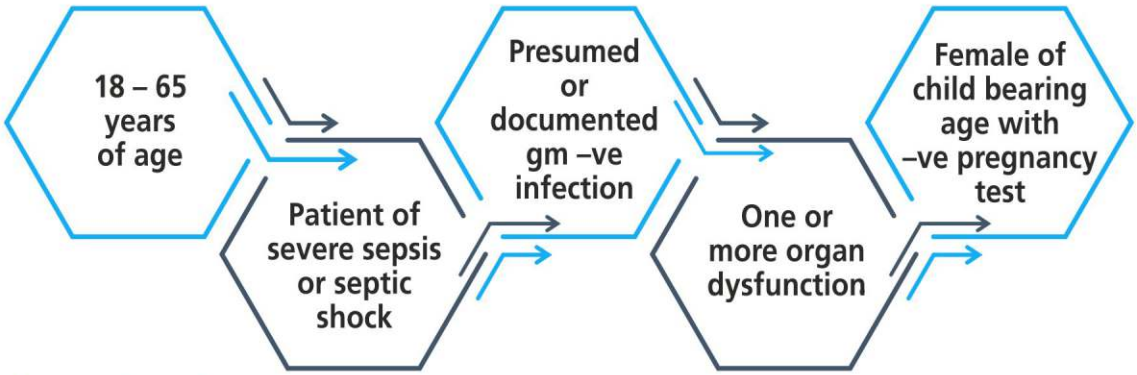
**Primary and Secondary Efficacy assessment**

**End of study visit: 28 days post randomization**

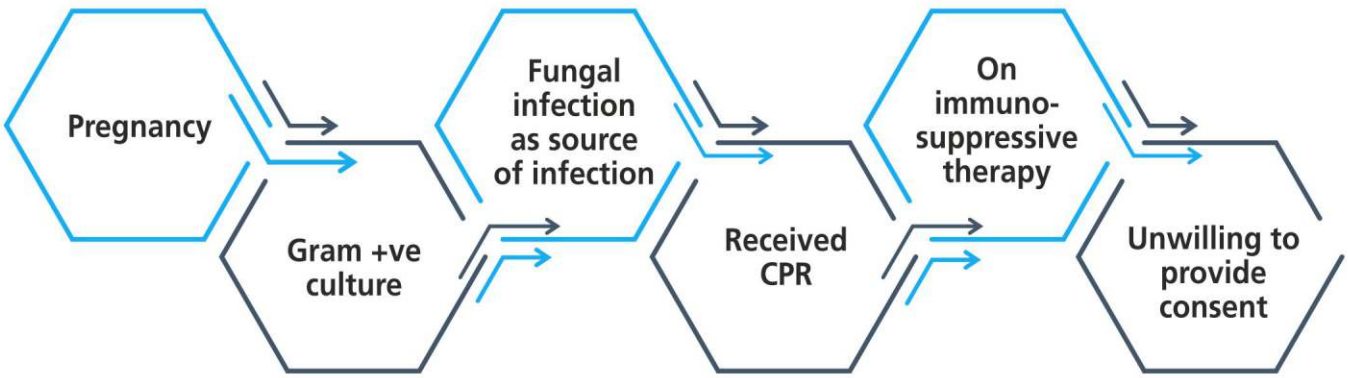
**Follow up study visit**

| Primary outcome | Secondary outcome |
|---|---|
| • 28-day all-cause mortality | • Delta SOFA scores<br>• Ventilator-free days<br>• Time-to-vasopressor withdrawal<br>• To assess safety/tolerability<br>• To assess emergent and recurrent infection rate |

## Inclusion Criteria



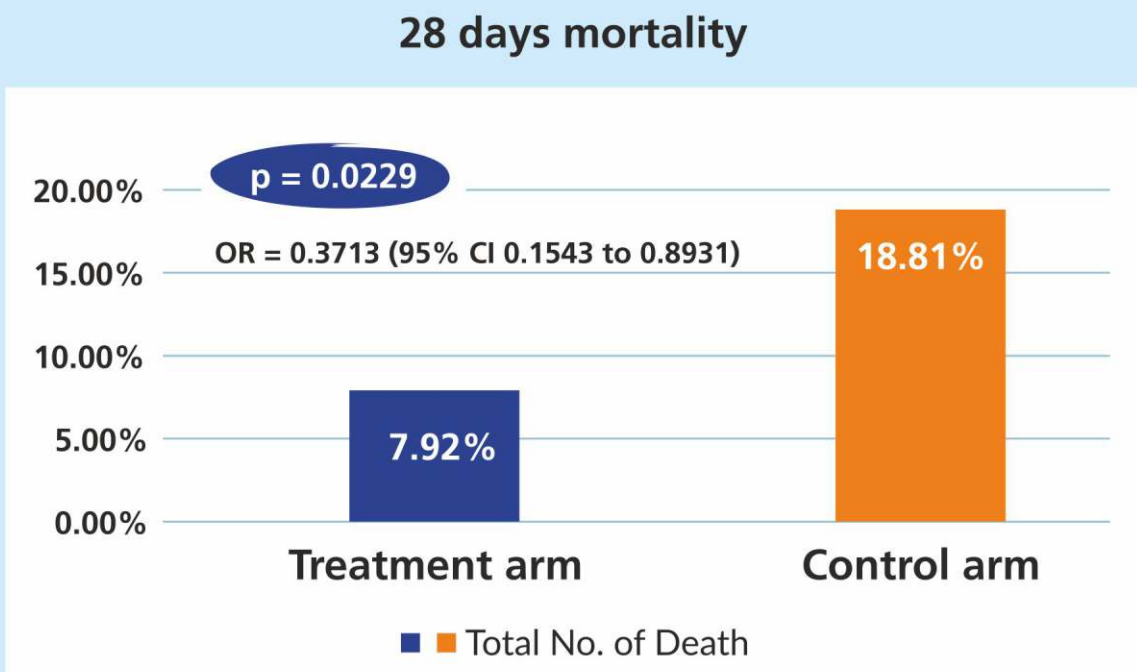

## Exclusion criteria




## Base line characteristics

| Parameters | Treatment Arm (N=101) | Control Arm (N=101) | p - value |
|---|---|---|---|
| Sex (Male/Female) | 49 / 52 | 45 / 56 | -- |
| Mean Age (Years) | 39.9 | 40.6 | 0.9896 |
| Mean Height (cm) | 159.2 | 159.1 | 0.39 |
| Mean Weight (kg) | 57.7 | 58.7 | 0.412 |
| Mean SOFA Score | 6.9 | 7.1 | 0.3416 |
| Patients in ICU | 101 | 101 | -- |
| Patients on Ventilator | 78 (77.23%) | 78 (77.23%) | 1 |
| Patients on Vasopressor | 46 (45.54%) | 50 (49.50%) | 0.573 |
| Patients with abnormal SGPT | 42 (41.58%) | 46 (45.54%) | 0.5703 |
| Patients with abnormal SGOT | 49 (48.51%) | 51 (50.50%) | 0.7784 |
| Patients with abnormal S. Creatinine | 38 (37.62%) | 30 (29.70%) | 0.2336 |

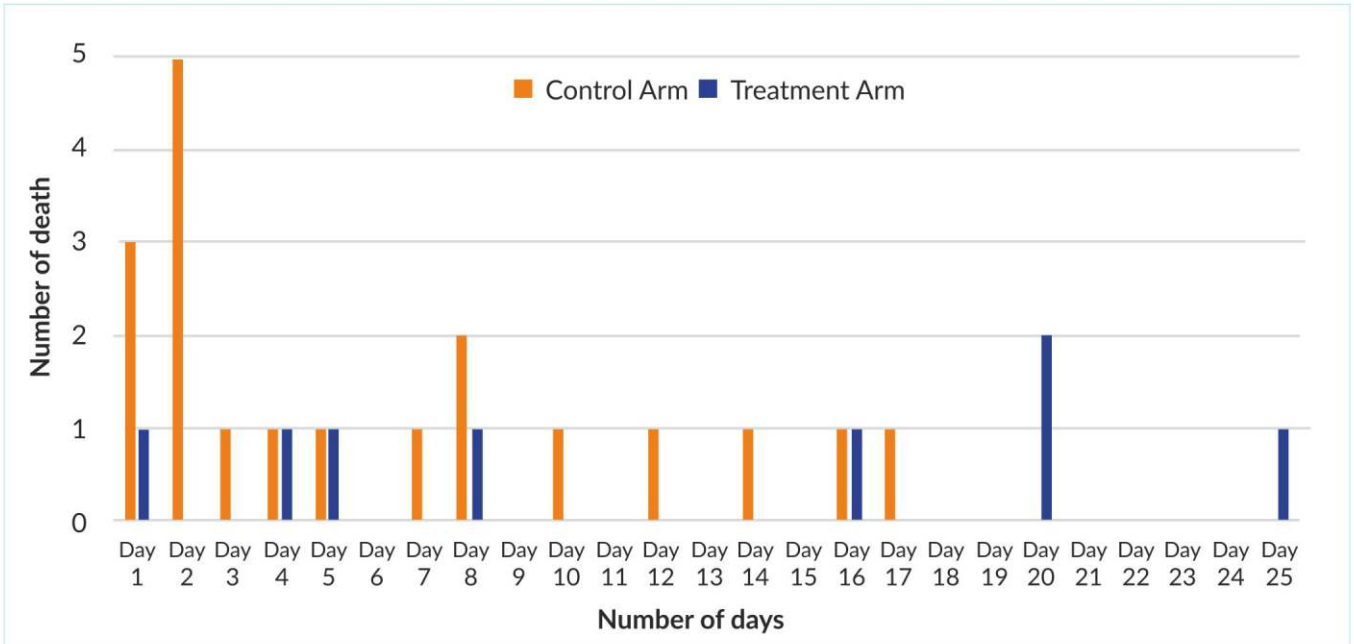
# **Results** Primary outcome




**Sepsivac provides a statistically significant (p=0.0229) reduction in mortality. 10.89% (absolute reduction) and 55.56% (relative reduction)**

| Treatment Arm | Total No. of patients enrolled | Total No. Death observed |
|---|---|---|
| Treatment Arm | 101 | 08 (7.92%) |
| Control Arm | 101 | 19 (18.81%) |
| Total | 202 | 27 (13.37%) |

## Days of Death in Treatment and Control Arm




# **Results** Secondary outcome

## Death as per the SOFA score

| Arm | All Patients | | SOFA Score <7 | | SOFA Score 7 | |
|---|---|---|---|---|---|---|
| | Died / Total Patients | % Died | Died / Total Patients | % Died | Died / Total Patients | % Died |
| Treatment Arm | 8/101 | 7.92 | 2/47 | 4.35 | 6/54 | 11.11 |
| Control Arm | 19/101 | 18.81 | 4/47 | 8.51 | 15/54 | 28.30 |
| Total | 27/202 | 13.37 | 6/94 | 6.45 | 21/108 | 19.63 |
| p value | 0.023 | - | - | 0.399 | 0.029 | - |

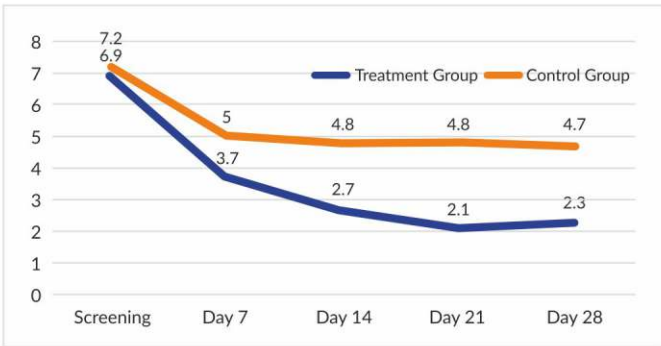
## Delays time to death

- Death was significantly delayed in the treatment arm compared to control arm.
- p-value: 0.0001, Hazard Ratio: 0.448 (95% CI: 0.311-0.646)

## Shortens Hospital Stay

- Time to discharge was significantly shorter in treatment arm for alive patients
- p-value: 0.0001, Hazard Ratio: 0.964 (95% CI: 0.948-0.981)

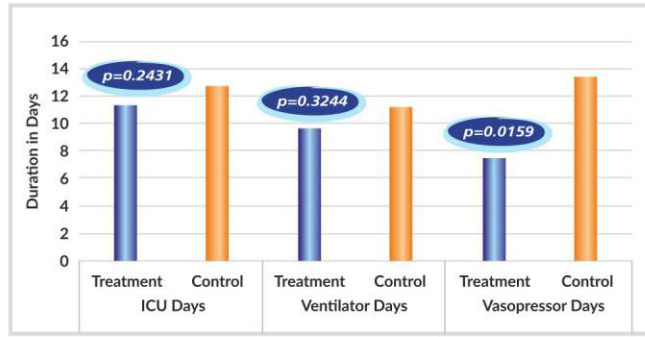
## Significantly reduces SOFA score




| p-value | 0.3416 | 0.0793 | 0.0182 | 0.0079 | 0.0181 |
|---|---|---|---|---|---|

**Change in SOFA score at day 14, 21 and 28**

## Duration of ICU stay, Ventilator and Vasopressor Treatment




**Requirement of Vasopressor administration is statistically less in the treatment arm**

## Baseline characteristics lab parameters (LFT and RFT)

| Day | SGPT | | | | SGOT | | | | SERUM CREATININE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T | % | C | % | T | % | C | % | T | % | C | % |
| **Normal** | 47 | 50.54 | 43 | 45.26 | 36 | 39.56 | 35 | 37.23 | 63 | 62.38 | 71 | 70.30 |
| **Abnormal** | 46 | 49.46 | 52 | 54.74 | 55 | 60.44 | 59 | 62.77 | 38 | 37.62 | 30 | 29.70 |
| **Abnormal Mean** | 553.21 | - | 254.22 | - | 585.60 | - | 313.53 | - | 3.37 | - | 2.92 | - |

## No. of patients having abnormal baseline values change to normal (at different time point)

| Day | SGPT | | | | SGOT | | | | SERUM CREATININE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T | % | C | % | T | % | C | % | T | % | C | % |
| **Screening** | 46 | 100 | 52 | 100 | 55 | 100 | 59 | 100 | 38 | 100 | 30 | 100 |
| **Normal Day 7*** | 10 | 21.74 | 01 | 1.92 | 08 | 14.55 | 01 | 1.69 | 16 | 42.11 | 11 | 36.67 |
| **Normal Day 14*** | 16 | 34.78 | 01 | 1.92 | 12 | 21.82 | 01 | 1.69 | 16 | 42.11 | 11 | 36.67 |
| **Normal Day 21*** | 20 | 43.48 | 01 | 1.92 | 14 | 25.45 | 01 | 1.69 | 16 | 42.11 | 13 | 43.33 |
| **Normal Day 28*** | 23 | 50.00 | 01 | 1.92 | 16 | 29.09 | 01 | 1.69 | 16 | 42.11 | 13 | 43.33 |
| p=value | ***0.0002*** | | | | ***0.0001*** | | | | ***0.9190*** | | | |

*T=Treatment Arm, C=Control Arm, *Cumulative*

# Conclusion

- Sepsivac addresses the therapy gap present in the treatment of sepsis
- Sepsivac offers a statistically significant (p=0.0229) reduction in mortality, 10.89% (absolute reduction) and 55.56% (relative reduction)
- Sepsivac reduces time to discharge from ICU and time to discontinue vasopressor treatment by effectively reducing SOFA score
- Sepsivac is a promising new entry as an adjuvant to standard care therapy for the management of gram negative sepsis

## Abridged Prescribing Information

Sepsivec Mycobacterium w (Heat Killed) Injection, 0.5 x 109 Cells
COMPOSITIONEach 0.1 mL contains: Mycobacterium w (Heat Killed):0.5 x 109 Cells, Sodium Chloride IP: 0.9 % w/v, Thiomersal IP: 0.01 % w/v, Water for injections IP : q.s INDICATIONS; Mycobacterium w (Heat Killed) injection is used as immunotherapeutic agent in the following disease conditions: Sepsis (due to gram Negative infections) - as adjuvant to the standard treatment. Leprosy – in Lepromin negative patients. Advanced Non-Small Cell Lung Cancer (NSCLC) - in combination with Paclitaxel plus Cisplatin regimen. DOSAGE AND ADMINISTRATION; Mycobacterium w (Heat Killed) injection is a sterile suspension for intradermal injection. The strength of Mycobacterium w (Heat Killed) injection is 0.5 x 109 Cells per 0.1 mL. A 0.3 ml of Mycobacterium w (Heat Killed) injection is given intradermally in three divided doses of 0.1 ml each on three different sites daily for three days. Total dose is 0.9 ml of Mycobacterium w over a period of three days. Mw (Heat Killed) injection is recommended to be prescribed in patient with age 18-65 years. CONTRAINDICATIONS; Mycobacterium w (Heat Killed) injection is contraindicated in: History of allergic reactions attributed to Mycobacterium w (Heat Killed) injection or any of the excipients in the formulation, Individuals with fever, Pregnant and Lactating women, Individuals with generalized septic skin conditions (if eczema exists, a site should be chosen that is free from skin lesions). Patient with chronic debilitating condition other than the proposed indication. WARNINGS AND PRECAUTION. Severe injection site reactions, large ulcers and abscess are most commonly caused by faulty injection technique. Hence adequate precaution should be taken while intradermal injections and should be administered by a healthcare staff well trained in the procedure. Mycobacterium w (Heat Killed) injection can cause erythema, induration and ulceration of the skin at site of injection which are usually mild and can be self-healing. If the condition is not cured then please consider supporting therapy and necessary antibiotics. Mycobacterium w (Heat Killed) injection is not recommended to be administer via Intravenous, subcutaneous, intramuscular injection. The intradermal injection can also cause minor active local reactions and local delayed type hypersensitivity reaction, type I and II reaction, neuritis. If condition get worsened or not self-cured please provide patient with proper supporting drug therapy. PREGNANCY AND LACTATION. Animal reproduction studies have not been conducted with Mycobacterium w (Heat Killed) injection. It is also not known whether Mycobacterium w (Heat Killed) injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. It is not known whether drug is excreted in human milk. As many drugs are excreted in human milk, caution should be exercised when drug is administered to a nursing woman. ADVERSE EFFECTS. It has been found to be generally well tolerated and free from severe systemic adverse effects in Leprosy treatment. The only side effects encountered were injection site erythema and ulceration. The erythema appeared after 48 hours of injection and was followed by induration by 7th day culminating into the formation of a shallow, self-healing ulcer in the 3rd week which healed with scab formation in the 4th week leaving a scar, as observed in clinical trials. Severe injection site reactions, large ulcers and abscesses are most commonly caused by faulty injection technique where part or the entire dose is administered too deeply. ISSUED ON: 14th Feb 2020; SOURCE: Prepared based on full prescribing information, version 2.0. Dated: Feb, 7th 2020: For full prescribing information, please contact: Medical Sciences Division, Cadila Pharmaceuticals Limited 1389, Trasad Road, Dholka, District – Ahmedabad, Gujarat Phone: +91-952714-221481/83/84

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