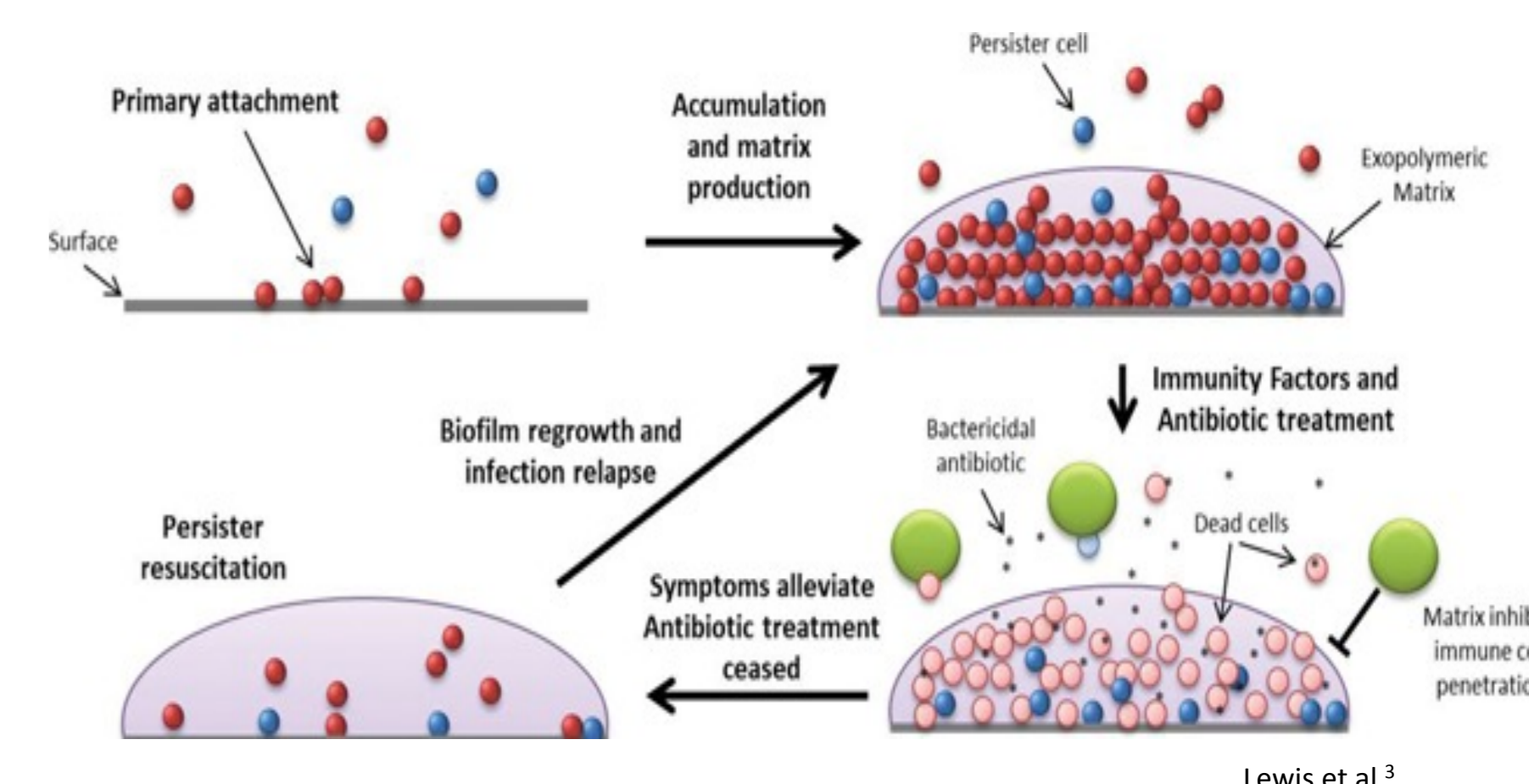


Staphylococcal bacteraemia: finding the path of least persistence

Background

- Despite the falling incidence of MRSA bacteraemia, the rate of MSSA bacteraemia is rising¹
- In a significant proportion of cases, bacteraemia persists despite appropriate therapy²
- Challenges to treatment arise as under the twin threats of antibiotics and the immune system, bacteria become dormant, metabolically inactive and are thus antibiotic tolerant³
- The regulator of the stress response in *S. aureus*, SigB, regulates entry into dormancy⁴



- **Aim: To characterise the role of SigB and its effector molecules in the survival of *S. aureus* in a clinical bacteraemia model**

The host environment modulates antibiotic susceptibility

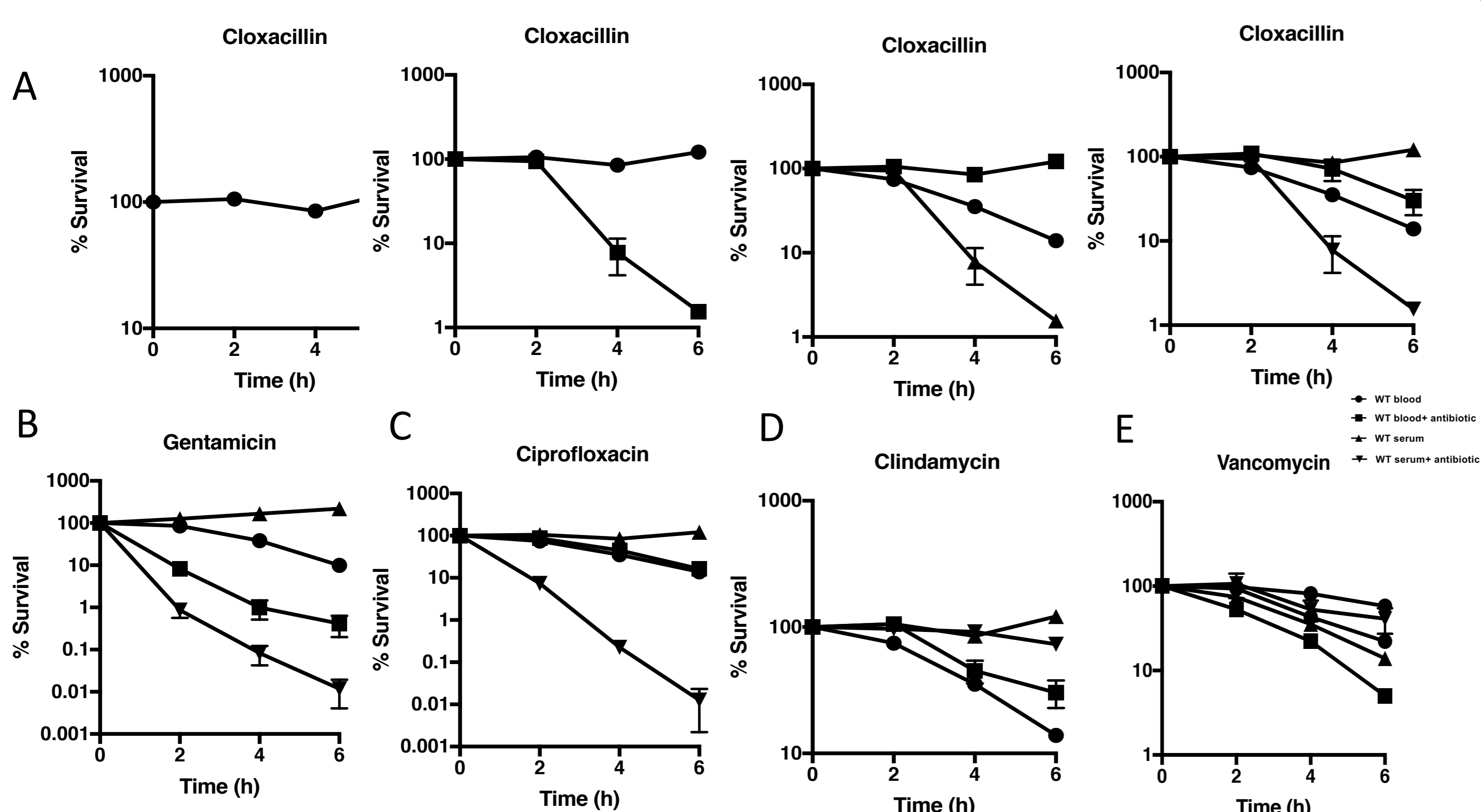


Figure 1. Blood modulates antibiotic susceptibility of *S. aureus* on exposure to Cloxacillin (A) Gentamicin (B), Vancomycin (C), Ciprofloxacin (D) Clindamycin (E). With the exception of (B) the addition of antibiotic failed to significantly enhance killing compared to blood alone, however antibiotics functioned in serum.

SigB promotes survival in blood

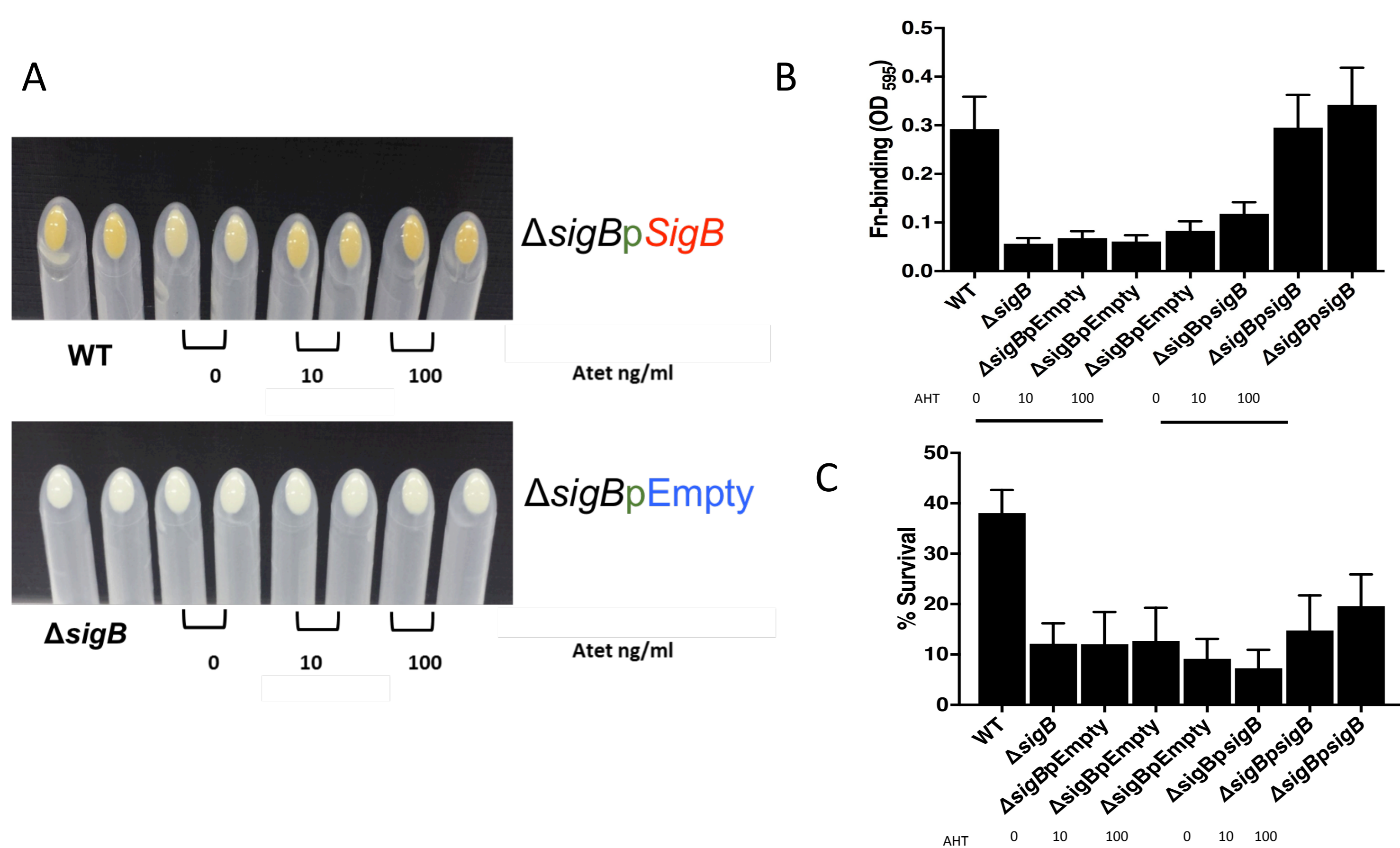


Figure 2. (A) Titrating concentration of AHT in the complemented *sigB* mutant resulted in increasing *sigB* expression, as evidenced by increase in pigment production and (B) fibronectin binding (both *sigB* dependent phenotypes). (C) Increasing survival of *S. aureus* in blood on increasing induction of *sigB* expression with AHT in complemented mutant but not in empty plasmid vector.

SigB modulates antibiotic susceptibility in the host context

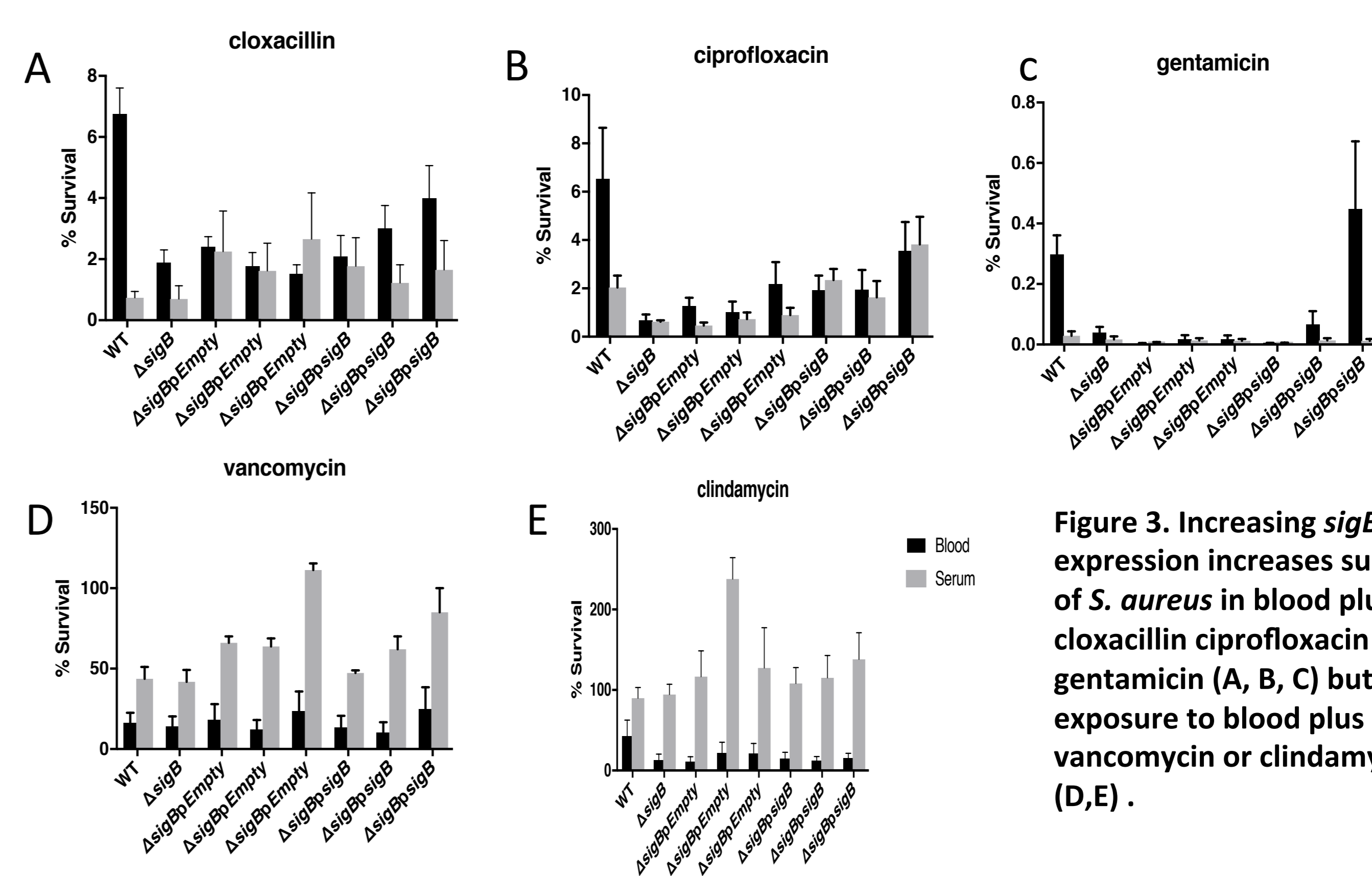


Figure 3. Increasing *sigB* expression increases survival of *S. aureus* in blood plus cloxacillin ciprofloxacin and gentamicin (A, B, C) but not on exposure to blood plus vancomycin or clindamycin (D, E).

SigB regulated genes modulate survival in blood +/- antibiotics

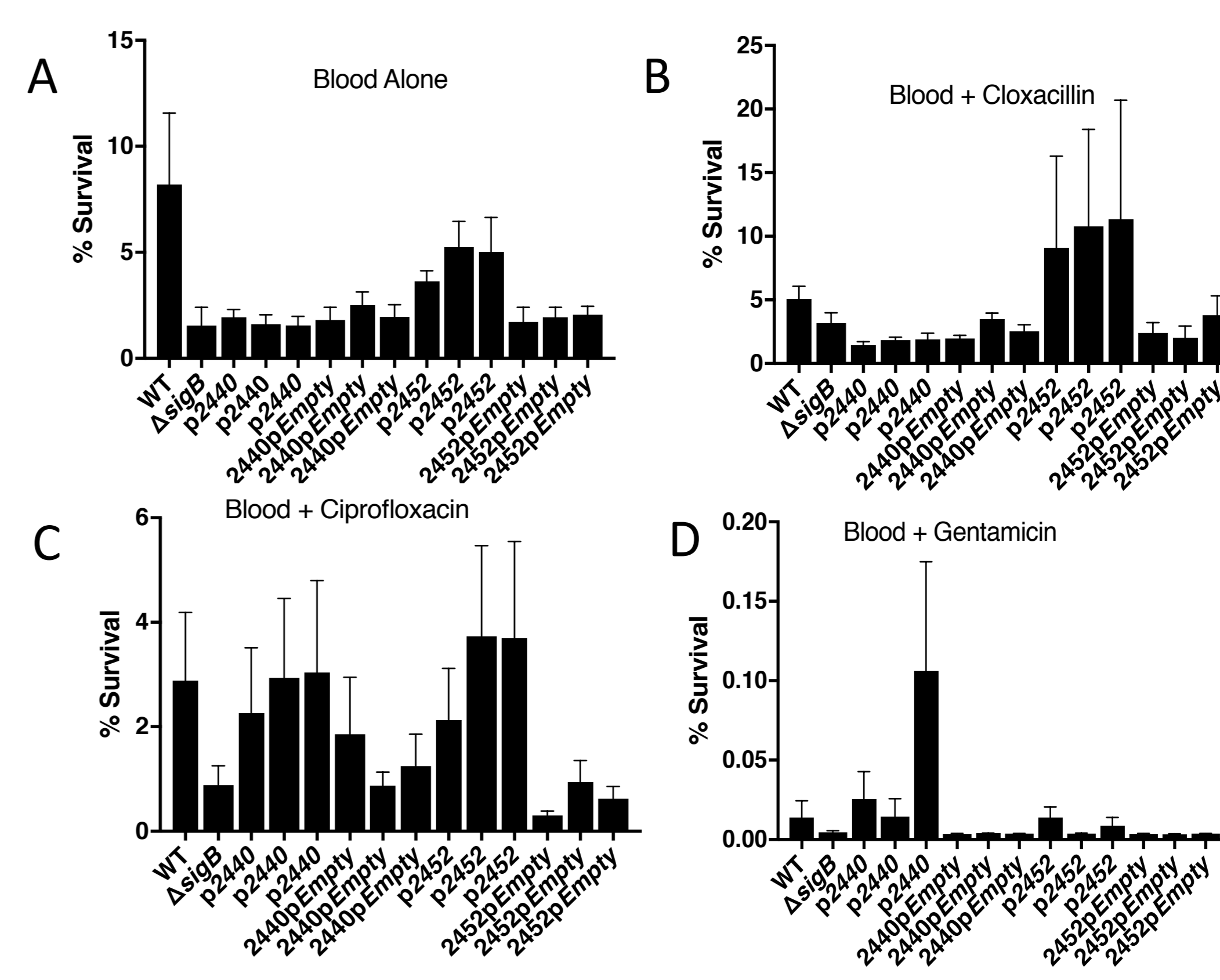
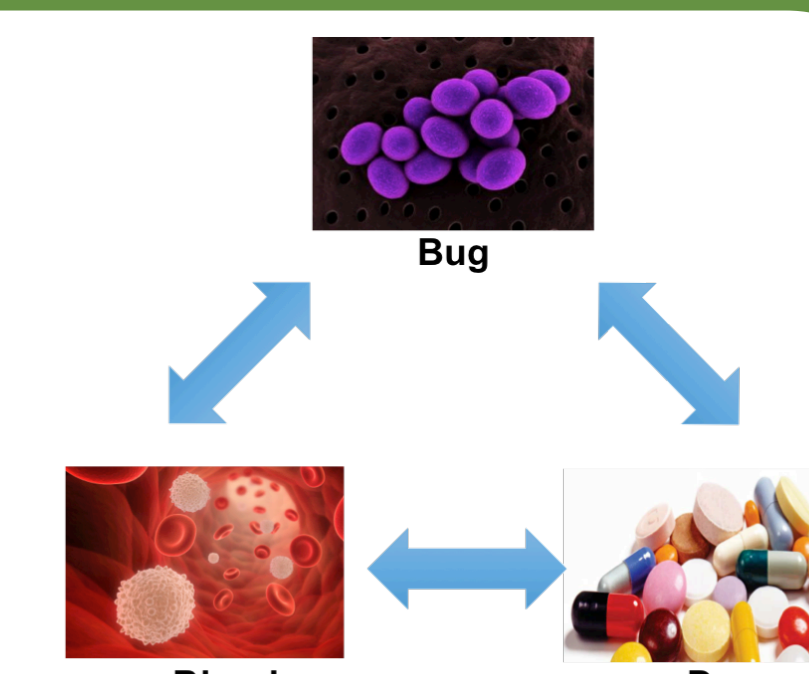


Figure 4. (A) *sigB* effectors SA2440 and SA2452 promote survival in blood infection model. Increasing expression of SA2452 but not SA2440 increases survival in blood alone (A) and in blood plus cloxacillin (B) in a dose dependent manner. Increasing expression of both genes increases survival on exposure to ciprofloxacin (C). SA2440 but not SA2452 promotes survival on exposure to gentamicin (D).

Conclusions

- Blood appears to have an inhibitory effect on the activity of certain antibiotics.
- SigB promotes survival in both blood alone plus in combination with cloxacillin, ciprofloxacin and gentamicin.
- Two SigB regulated genes have been identified that promote survival in an antibiotic specific manner.
- Rethinking therapy in the context of the host-pathogen-drug interactions may lead to innovative solutions to enhance existing treatment strategies.



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