INTRODUCTION
Hydroxyethyl starch (HES) fluid resuscitation has recently been demonstrated to increase in mortality and acute kidney injury in patients with septic shock. It is unclear whether an analysis of preclinical HES studies may have helped predict the adverse effects of these fluids. We therefore conducted a preclinical systematic review and meta-analysis to investigate the safety of HES compared to other resuscitation fluids in animal models of sepsis. Here we report on the outcome of mortality.

METHODS
A systematic search of Ovid MEDLINE and Embase was performed in collaboration with an information specialist (inception-01/2015). Citations were screened independently in duplicate. Studies comparing HES vs other resuscitation fluid in preclinical in vivo sepsis models were included. The Cochrane Risk of Bias Assessment Tool was used to assess internal validity of each included study. Construct validity (i.e. clinical generalizability) was assessed using a previously proposed 8 point framework. Results are expressed as risk ratios (RR) and 95% confidence intervals (95% CI). Meta-analysis was performed using an inverse variance random effects model. A priori determined outcome ascertainment windows were also analyzed (≤2 days, 2-4 days, ≥4 days).
RESULT
10 articles met eligibility criteria (n=439 animals). Animal models included rat (5 studies), swine (3), and sheep (2). To model disease, studies used IV endotoxin (4), cecal ligation and puncture (3), live bacteria implant (1), live bacteria infusion (1), and fecal peritonitis (1). Comparison fluids included gelatin (5), ringer's lactate/acetate (5), saline (3), sterofundin (2), albumin (1), and pig plasma (1). Risk of bias was variable: 8 studies reported randomizing but did not describe the method, no studies described allocation concealment, personnel and outcome assessment were low risk of bias in 4 and 2 studies, respectively. Studies incorporated a median of 2 (range 1-4) of 8 suggested construct validity criteria to increase clinical relevance (e.g. no studies included animals with comorbidities). Mortality of animals was described in 6 studies and no statistically significant effect of HES on mortality was noted (RR 1.45, 95%CI 0.75-2.75, $I^2 = 43\%$). One study reported on animals ≥4 days, with 7/7 animals treated with HES and 0/7 treated with plasma dying, respectively.

CONCLUSION
There is a paucity of preclinical evidence regarding the long term safety of HES in animal models of sepsis. Available evidence suffered from variably risk of bias and potentially lower construct validity. Pooled analysis suggested a non-significant trend towards harm with HES. The single study performed with a longer outcome ascertainment window demonstrated harm with HES.

References:
1. JAMA 2013 309:678-688
2. Crit Care Med 2010 38:2401-2408