

Author's response to commentary on the PHANTASi trial

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Bolliger R, Merker M, Schuetz P. Use of antibiotics in the ambulance for sepsis patients: is earlier really better? *J Thorac Dis* 2018;10:1239-41.

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We read, with interest, the letters to editor by Rello *et al.* (1) and Bolliger *et al.* (2) in response to our Prehospital Antibiotics Against Sepsis (PHANTASi) trial which was recently published in the *Lancet Respiratory Medicine* (3).

Bolliger *et al.* states that a limitation of the PHANTASi trial is that it is less comparable with previous studies, due to the fact that the study population in the PHANTASi trial consisted of patients screened in the ambulance with varying degrees of sepsis, whereas other studies focused on intensive care unit (ICU) patients with septic shock. We agree that the study population differs from previous studies; however, the aim of our study was to include a representative sample of sepsis patients presenting at the emergency department (ED), since patients who are admitted to an ICU are essentially different from a general ED population. A prior study in the Netherlands which investigated the epidemiology of sepsis patients in the Netherlands found that nearly half of all sepsis patients presenting to the ED were transported by emergency medical services (EMS), and that those who were transported by EMS were more seriously ill, than those who were transported otherwise (4). Therefore, we found that a study population consisting of sepsis patients that were transported by EMS personnel was a representative sample of the general sepsis population.

Both commentators state correctly, that we used SEPSIS-2 criteria for the inclusion of sepsis, and that the use of the quick Sepsis-related Organ Failure Assessment

(qSOFA) criteria would make some patients in our study not eligible for inclusion. At the time of the initiation of the PHANTASi trial, the systemic inflammatory response syndrome (SIRS) criteria were used to diagnose sepsis in the ambulance. Moreover, the disease severity of our included population is highlighted by the fact that 80% of the patients who were included in our study, had a National Early Warning Score (NEWS) ≥ 5 . This was the case in both the control and the intervention arm.

A recent study found that for the prediction of in-hospital mortality of sepsis patients, qSOFA has a higher specificity than SIRS, but a lower sensitivity than the SIRS (5). Considering the fact that a high sensitivity is important, when patients who have a serious yet treatable disease, need to be identified, the value of qSOFA in the ED setting is still a subject of debate and qSOFA needs to be validated prospectively in the pre-hospital and ED setting.

Rello *et al.* raises the concern that the group of patients with organ dysfunction in the PHANTASi trial comprises a small proportion. However, 57% of patients had organ dysfunction with severe sepsis while 4% had septic shock. The sepsis severity that was used in our study, was categorized into three groups according to the 2001 SCCM/ESCIM/ACCP/ATS/SIS International Sepsis Definitions Conference guidelines (6). These guidelines define severe sepsis as “sepsis complicated by organ dysfunction”. Therefore, not a small proportion but rather the majority of

our included patients had organ dysfunction.

Although we agree with the commentator that shortening of the time to antibiotics (TTA) in the intervention group of the PHANTASi trial did not lead to significant advantages in patient survival rates, we want to highlight that the TTA was shortened by 96 minutes in our study instead of the 26 minutes as the commentator has mistakenly mentioned.

Rello *et al.* makes a valid point by arguing that the use of antibiotics in the ambulance might be more critical in immune-compromised patients. Nearly 14% of the patients in both the intervention and control arm in our study had experienced a form of malignant cancer in the past 5 years or were currently under treatment for a form of malignant cancer. We are currently analyzing the data of these immunocompromised patients regarding the effect of prehospital antibiotics.

We agree with the commentators that training of EMS personnel is important (1,2) and that the development and implementation of educational programs for the recognition and treatment of sepsis, should be a priority (1). A study which was conducted in the Netherlands, prior to the start of the PHANTASi trial, found an in-hospital mortality rate of 21% for septic patients who were transported by EMS (7), which was higher than the in-hospital mortality rate of 6% in the PHANTASi trial. During the PHANTASi trial, sepsis awareness was increased by training Dutch EMS personnel in the recognition of sepsis. Furthermore, we also increased awareness on a national level, by the use of social media, and mass media channels. This training, and increased awareness, may have strengthened the acute care chain, and might have led to the far lower, in-hospital mortality rate, in our study. In the Netherlands the efforts of our study team have led to the implementation of sepsis as a mandatory part of the study course material of EMS personnel.

As Rello *et al.* (1) already mentioned, excessive use of antibiotics should always be avoided, due to the risk of antibiotic resistance. This is especially important with the ageing population, and the consequently increasing numbers of patients presenting to the ED during the flu season. These patients often receive antibiotics despite having a viral infection. This also highlights the importance of training medical personnel in the recognition of sepsis, as well as the added value of developing and/or validating sepsis biomarkers, as already pointed out by both commentators (1,2).

In both letters (1,2), the authors express three concerns regarding the generalizability of the findings of the PHANTASi trial to other countries and situations. The Netherlands has a well-organized general practitioner

system, short dispatch times, and the study had a small proportion of septic shock patients.

We agree that whether the inclusion of more septic shock patients in a situation with longer dispatch times and/or a less organized general practitioner system could have led to a different result. We are currently investigating the option of an international follow-up study including only septic shock patients in order to answer these questions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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