An innovative telemedical network to improve infectious disease management in critically ill patients and outpatients: a stepped-wedge, cluster randomized controlled trial (TELnet@NRW)

Gernot Marx, Wolfgang Greiner, Christian Juhra, Svenja Elkenkamp, Daniel Gensorowsky, Sebastian W Lemmen, Jan Englbrecht, Sandra Dohmen, Antje Gottschalk, Miriam Haverkamp, Annette Hempen, Christian Flügel-Bleienheuft, Daniela Bause, Henna Schulze-Steinen, Susanne Rademacher, Jennifer Kistermann, Stefan Hoch, Hans-Jürgen Beckmann, Christian Lanckohr, Volker Lowitsch, Arne Peine, Fabian Juzek-Kuepper, Carina Benstoem, Kathrin Sperling, Robert Deisz

Submitted to: Journal of Medical Internet Research on: October 06, 2021

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressively prohibit redistribution of this draft paper other than for review purposes.
# Table of Contents

**Original Manuscript**

| Topic                                      | Page |
|---------------------------------------------|------|
| Supplementary Files                         | 28   |
| Figures                                     | 29   |
| Figure 1                                    | 30   |
| Figure 2                                    | 31   |
| Multimedia Appendixes                       | 32   |
| Multimedia Appendix 1                       | 33   |
| Multimedia Appendix 2                       | 33   |
| Multimedia Appendix 3                       | 33   |
| Multimedia Appendix 4                       | 33   |
| Multimedia Appendix 5                       | 33   |
| Multimedia Appendix 6                       | 33   |
| Multimedia Appendix 7                       | 33   |
| Multimedia Appendix 8                       | 33   |
| Multimedia Appendix 9                       | 33   |
| Multimedia Appendix 10                      | 33   |
| Multimedia Appendix 11                      | 33   |
| CONSORT (or other) checklists               | 34   |
| CONSORT (or other) checklist 0              | 34   |

https://preprints.jmir.org/preprint/34098 [unpublished, peer-reviewed preprint]
An innovative telemedical network to improve infectious disease management in critically ill patients and outpatients: a stepped-wedge, cluster randomized controlled trial (TELnet@NRW)

Gernot Marx¹; Wolfgang Greiner²; Christian Juhra³; Svenja Elkenkamp²; Daniel Gensorowsky²; Sebastian W Lemmen¹; Jan Englbrecht¹; Sandra Dohmen¹; Antje Gottschalk³; Miriam Haverkamp¹; Annette Hempen³; Christian Flügel-Bleienheuft⁶; Daniela Bause³; Henna Schulze-Steinen⁴; Susanne Rademacher⁴; Jennifer Kistermann⁴; Stefan Hoch⁶; Hans-Jürgen Beckmann⁵; Christian Lanckohr³; Volker Lowitsch⁷; Arne Peine³; Fabian Juzek-Kuepper³; Carina Benstoem⁴; Kathrin Sperling³; Robert Deisz⁴

¹University Hospital RWTH Aachen Aachen DE
²Bielefeld University Bielefeld DE
³University Hospital Muenster Muenster DE
⁴Medical Faculty RWTH Aachen Aachen DE
⁵Physician Network, Medizin und Mehr eG (MuM) Buende DE
⁶Physician Network, Gesundheitsnetz Köln-Süd (GKS) e.V. Cologne DE
⁷Healthcare IT Solutions GmbH Aachen DE

these authors contributed equally

Corresponding Author:
Gernot Marx
University Hospital RWTH Aachen
Pauwelsstr. 30
Aachen
DE

Abstract

Background: Evidence-based infectious disease and intensive care management is more relevant than ever. Medical expertise in the two disciplines is often geographically limited to university institutions. In addition, the interconnection between inpatient and outpatient care is often insufficient (e.g., no shared electronic health record, no digital transfer of patient findings).

Objective: To establish and evaluate a telemedical inpatient-outpatient network based on expert teleconsultations to increase treatment quality in intensive care medicine and infectious diseases.

Methods: We performed a multicentre, stepped-wedge cluster randomised trial (Feb 2017 – Jan 2020) to establish a telemedicine inpatient-outpatient network among university hospitals, hospitals, and outpatient physicians in North Rhine Westphalia, Germany. Patients ≥ 18 years of age in the intensive care unit (ICU) or consulting with a physician in the outpatient setting were eligible. We provided expert knowledge from intensivists and infectious disease specialists through advanced training courses and expert teleconsultations with 24/7/365 availability on demand resp. once per week to enhance treatment quality. The primary outcome was adherence to the ten Choosing Wisely® recommendations for infectious disease management. Guideline adherence was analysed using binary logistic regression models.

Results: Overall, 159,424 patients (10,585 inpatients, 148,839 outpatients) from 17 hospitals and 103 outpatient physicians were included. There was a significant increase in guideline adherence in the management of Staphylococcus aureus infections (OR 4.00 [95% CI 1.83, 9.20], P<.01) and in sepsis management in critically ill patients (OR 6.82 [95% CI 1.27, 56.61], P=.04). Sepsis related mortality was reduced from 28.8% (19/66) in the control group to 23.8% (50/210) in the intervention group (P=.37). Furthermore, the extension of treatment with prophylactic antibiotics after surgery was significantly less likely (OR 9.37 [95% CI 1.52, 111.47], P=.04). Patients treated by outpatient physicians, who were regularly taking part in expert teleconsultations, were also more likely to be treated according to guideline recommendations regarding antibiotic therapy for uncomplicated upper respiratory tract infections (OR 1.34 [95% CI 1.16, 1.56], P<.01) and asymptomatic bacteriuria (OR 9.31 [95% CI 3.79, 25.94], P<.01). For the other recommendations, we found no significant effects, or we had too few observations to generate models.

https://preprints.jmir.org/preprint/34098 [unpublished, peer-reviewed preprint]
**Conclusions:** Telemedicine facilitates a direct round-the-clock interaction over broad distances between intensivists or infectious disease experts and physicians who care for patients in hospitals without ready access to these experts. Expert teleconsultations increase guideline adherence and treatment quality in infectious disease and intensive care management creating added value for critically ill patients. Clinical Trial: ClinicalTrials.gov, NCT03137589

(JMIR Preprints 06/10/2021:34098)

DOI: https://doi.org/10.2196/preprints.34098

**Preprint Settings**

1) Would you like to publish your submitted manuscript as preprint?

   ✔ No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

   ✔ Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).

   Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.

   Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in the PubMed Now! service, my accepted manuscript PDF will automatically be made openly available.

https://preprints.jmir.org/preprint/34098 [unpublished, peer-reviewed preprint]
Original Manuscript
An innovative telemedical network to improve infectious disease management in critically ill patients and outpatients: a stepped-wedge, cluster randomized controlled trial (TELnet@NRW)

Gernot Marx¹, Wolfgang Greiner², Christian Juhra³, Svenja Elkenkamp², Daniel Gensorowsky², Sebastian W. Lemmen⁴, Jan Englbrecht⁵, Sandra Dohmen¹, Antje Gottschalk⁵, Miriam Haverkamp⁴, Annette Hempen⁶, Christian Flügel-Bleienheuft⁷, Daniela Bause⁵, Henna Schulze-Steinen¹, Susanne Rademacher¹, Jennifer Kistemmann¹, Stefan Hoch⁷, Hans-Jürgen Beckmann⁶, Christian Lanckohr⁸, Volker Lowitsch⁹, Arne Peine¹, Fabian Juzek-Kuepper⁴, Carina Benstoem¹, Kathrin Sperling⁵*, Robert Deisz¹* and the TELnet Study Group

¹ Department of Intensive Care Medicine, Medical Faculty RWTH Aachen, Aachen, Germany
² Department of Health Economics and Health Care Management, Bielefeld University, Bielefeld, Germany
³ Office of eHealth, University Hospital Muenster, Muenster, Germany
⁴ Department for Infectious Diseases and Infection Control, Medical Faculty RWTH Aachen, Aachen, Germany
⁵ Department of Anaesthesiology, Intensive Care Medicine and Pain Medicine, University Hospital Muenster, Münster, Germany
⁶ Physician Network, Medizin und Mehr eG (MuM), Buende, Germany
⁷ Physician Network, Gesundheitsnetz Köln-Süd (GKS) e.V., Cologne, Germany
⁸ Institute of Hygiene, University Hospital Muenster, Münster, Germany
⁹ Healthcare IT Solutions GmbH, Aachen, Germany

Corresponding author:
Prof. Dr. Gernot Marx, FRCA
Department of Intensive Care Medicine and Intermediate Care
Medical Faculty RWTH Aachen
Pauwelsstr. 30
D - 52074 Aachen
Phone: +49 241 80-80444
Fax: +49 241 80-3380444
gmarx@ukaachen.de

Abstract
Background
Evidence-based infectious disease and intensive care management is more relevant than ever. Medical expertise in the two disciplines is often geographically limited to university institutions. In addition, the interconnection between inpatient and outpatient care is often insufficient (e.g., no shared electronic health record, no digital transfer of patient findings).

Objectives
To establish and evaluate a telemedical inpatient-outpatient network based on expert
Methods
We performed a multicentre, stepped-wedge cluster randomised trial (Feb 2017 – Jan 2020) to establish a telemedicine inpatient-outpatient network among university hospitals, hospitals, and outpatient physicians in North Rhine Westphalia, Germany. Patients ≥ 18 years of age in the intensive care unit (ICU) or consulting with a physician in the outpatient setting were eligible. We provided expert knowledge from intensivists and infectious disease specialists through advanced training courses and expert teleconsultations with 24/7/365 availability on demand resp. once per week to enhance treatment quality. The primary outcome was adherence to the ten Choosing Wisely® recommendations for infectious disease management. Guideline adherence was analysed using binary logistic regression models.

Results
Overall, 159,424 patients (10,585 inpatients, 148,839 outpatients) from 17 hospitals and 103 outpatient physicians were included. There was a significant increase in guideline adherence in the management of Staphylococcus aureus infections (OR 4.00 [95% CI 1.83, 9.20], P<.01) and in sepsis management in critically ill patients (OR 6.82 [95% CI 1.27, 56.61], P=.04). There was a statistically non-significant decrease in sepsis related mortality from 28.8% (19/66) in the control group to 23.8% (50/210) in the intervention group. Furthermore, the extension of treatment with prophylactic antibiotics after surgery was significantly less likely (OR 9.37 [95% CI 1.52, 111.47], P=.04). Patients treated by outpatient physicians, who were regularly taking part in expert teleconsultations, were also more likely to be treated according to guideline recommendations regarding antibiotic therapy for uncomplicated upper respiratory tract infections (OR 1.34 [95% CI 1.16, 1.56], P<.01) and asymptomatic bacteriuria (OR 9.31 [95% CI 3.79, 25.94], P<.01). For the other recommendations, we found no significant effects, or we had too few observations to generate models. Key limitations of our study include selection effects due to the applied on-site triage of patients as well as the limited possibilities to control for secular effects.

Conclusions
Telemedicine facilitates a direct round-the-clock interaction over broad distances between intensivists or infectious disease experts and physicians who care for patients in hospitals without ready access to these experts. Expert teleconsultations increase guideline adherence and treatment quality in infectious disease and intensive care management creating added value for critically ill patients.

Registration
ClinicalTrials.gov, NCT03137589, https://clinicaltrials.gov/ct2/show/NCT03137589

Keywords
Telemedicine; Infectious Disease Medicine; Sepsis; Evidence-Based Medicine; eHealth
Introduction

Worldwide, health workforce shortages are a pressing concern. By 2030, it is estimated that there will be a shortage of 9.9 million physicians and nurses worldwide [1,2]. Additionally, the proportion of elderly people in Europe will exceed 30% by 2050 [3,4]. Hence, healthcare systems must become more flexible and efficient, e.g., through accelerated digitisation. Infectious disease management, especially the management of sepsis, is one area in which the potential for digitisation to reduce the global burden of disease is particularly strong.

Increasing antimicrobial resistance (AMR) poses a growing threat to patients. Important underlying drivers are the overuse and misuse of antibiotics. Every year, approximately 700,000 patients worldwide die from infections that are treatable with antibiotics [5]. Global pandemics such as COVID-19 are likely to promote the overuse of antimicrobials, thereby facilitating the further development of AMR. AMR could cost US$100 trillion between now and 2050, with the annual mortality rate reaching 10 million over this period [5].

In 2017, there were approximately 48.9 million cases of sepsis worldwide and 11 million sepsis-related deaths (19.7% of all deaths globally) [6]. Sepsis is the most common cause of morbidity and mortality in ICUs around the world. Although the sepsis-related mortality rate is continuously decreasing, it is still remarkably high (30-50%) [7-9]. The associated costs are US$24 billion annually in the US alone [6].

Numerous studies have shown that adherence to clinical practice guidelines for antibiotic therapy and sepsis management is associated with improved patient outcomes [10-15]. Alarmingly, compliance with these guidelines is low [10,16-18]. International educational healthcare campaigns, such as the Choosing Wisely® initiative, have responded to this global challenge by increasing professional awareness of evidence-based medicine [19]. In general, the Choosing Wisely® recommendations promote essential practices and the avoidance of unnecessary diagnostic, preventive, and therapeutic procedures [15,19].

Telemedicine has the potential to support these efforts. It facilitates direct, round-the-clock interactions between physicians who care for patients in hospitals with limited sub-specialist staff and intensivists or infectious disease specialists located far away. Observational studies have demonstrated that expert teleconsultations can reduce sepsis-related mortality by approximately 25%, with a simultaneous increase in guideline adherence [12,20]. Despite decades of intensive care research worldwide, no drug or other therapeutic measure has achieved a comparable reduction. The aim of TELnet@NRW was to establish and evaluate a telemedical inpatient-outpatient network (24/7/365) to improve the application of evidence-based medicine in infectious disease management, especially the management of sepsis. We hypothesised that the establishment of a digital network based on expert teleconsultations increases treatment quality in inpatient and outpatient care for these two subspecialties.

Methods

Trial design

TELnet@NRW was a multicentre, stepped-wedge cluster randomized trial conducted at two university hospitals (Aachen and Muenster), 17 hospitals and 103 outpatient physicians’ offices associated with two physician networks. The study protocol is publicly available [21], and the trial was prospectively registered at ClinicalTrials.gov (NCT03137589). The Ethics Committee of the Medical Faculty of the RWTH Aachen approved the study (EK 068/17). The study was funded by the Innovation Fund of the Federal Joint Committee (Feb 2017 – Jan 2020, funding code 01 NVF16010). Independent researchers from the Department of Health Economics and Health Care
Management at Bielefeld University conceptualized and performed the analyses. The reporting of this trial is in line with the CONSORT-EHEALTH checklist [22].

Inpatient and outpatient participants

Inpatients, 18 years of age or older, who had *Staphylococcus aureus* bacteraemia and/or required intensive care treatment and who provided written informed consent were eligible for inclusion. Outpatients, 18 years of age or older, with a possible infectious presentation based on the International Classification of Primary Care, who provided written informed consent were eligible for enrolment. Measles vaccination rates in children were also evaluated. Due to the complexity and diversity of possible diagnoses and the extremely high total number of patients during the entire study period, triage for study enrolment was carried out by the attending physician on site. We excluded minors and patients who did not formally consent to participate in the study. Additionally, patients who were in a dependent or employment relationship with the sponsor or one of the investigators/the principal investigator and patients who lived in an institution as mandated by a legal or administrative order were excluded from the study.

Technical requirements

Initially, the standardised technical requirements at each participating site were established in line with the relevant guideline recommendations [23]. This also included setting up a wireless local area network (WLAN) in hospitals and medical practices. A secure, privacy-compliant infrastructure was used for communication, including two high-encryption audio-video conference systems and the certified data exchange platforms *FallAkte Plus* and *ELVI*, which complied with the General Data Protection Regulation (EU Regulation 2016/679). Overall, our data protection measures were externally reviewed by independent data protection experts and continuously monitored throughout the study. The video conferencing infrastructure met high requirements in terms of quality, data security and portability. This infrastructure operated in a high-security, closed network (hardware VPN) or on dedicated lines.

Interventions: Expert teleconsultations plus advanced training courses

The innovative telemedical network TELnet@NRW involved outpatient-inpatient cooperation. Separate facilities (hospitals of different levels of care and outpatient physicians’ offices) established a new digital healthcare structure for North Rhine Westphalia, Germany. TELnet@NRW provided expert knowledge from two university hospitals to participating hospitals and outpatient physicians through expert teleconsultations (24/7/365 availability). Expert teleconsultations were provided on request after the initial triage was carried out by the attending physician on site. Consultants for intensive care medicine participated in key care processes 24/7, whereas infectious disease specialists were available once weekly and on demand, including participation in rounds, additional expert teleconsultations, emergency consultations and audits of clinical patient data. Before implementation of the expert teleconsultations, participants received advanced training courses on guideline-compliant treatment.

Study schedule and data collection

All clusters went through three different study phases: During the pre-intervention phase pseudonymised patient data from routine care was documented (details are provided in Multimedia appendix 1: Study schedule using a stepped-wedge design (inpatient sector; and Multimedia
appendix 2: Study schedule using a stepped-wedge design (outpatient sector), pre-intervention phase shown in red). During the subsequent transition phase (shown in white), the required hardware infrastructure was set up at the different study sites. Then, participants received on-site training according to their cluster schedule. To familiarize participants with the new processes, expert teleconsultations were already provided during the transition phase. Data on the effects of the intervention were collected during the following intervention phase (shown in blue). Primary data were generated using standardised case reporting forms. For the analyses of influenza and measles vaccination rates, we used routine outpatient claims data from the Association of Statutory Health Insurance Physicians (AHIP).

Outcomes

The primary outcome measure was adherence to the ten Choosing Wisely® recommendations for infectious diseases provided by the German Society for Infectious Diseases, which are applicable to both inpatient and outpatient care; these contain five “Dos” and “Don’ts” for infectious disease management (for each definition please refer to Multimedia appendix 3: Analysis algorithms of the 10-Choosing Wisely Recommendations) [15]. Notably, the first two “Dos” address important quality indicators in intensive care medicine as they are associated with lower mortality [12,20,24,25]. For improved overview, Table 1 shows the 10-Choosing Wisely Recommendations sorted by their applicability to the inpatient and outpatient sector.

Table 1 – Primary outcome sorted by sector

| Primary outcome inpatient sector: Adherence to the following Choosing-Wisely recommendations | Primary outcome outpatient sector: Adherence to the following Choosing-Wisely recommendations |
|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| *Staphylococcus aureus* bloodstream infection imperatively needs efficacious antimicrobial treatment and identification and elimination of the source of infection. (P1) | Annual influenza vaccination should be given to individuals aged >60 years, patients with specific co-morbidities and people (e.g., health care workers) who may infect vulnerable persons (P3) |
| In critically ill patients with signs of infection, early appropriate antibiotic therapy is crucial after obtaining cultures, and treatment should be regularly re-evaluated (P2) | All children should receive the measles vaccine, and adults born after 1970 without prior documented vaccination against measles should get at least one dose of the vaccine (P4) |
| Prescribe oral forms of highly bioavailable antimicrobial agents to patients who can reliably receive and absorb medications via the enteral route (P5) | Avoid prescribing antibiotics for uncomplicated upper respiratory tract infections including bronchitis (N1) |
| Do not treat asymptomatic bacteriuria with antibiotics (N2) | Do not treat asymptomatic bacteriuria with antibiotics (N2) |
| Do not treat Candida recovered from respiratory or gastrointestinal tract specimens (N3) | Do not extend the administration of prophylactic antibiotics after surgery (after the patient has left the operating room) (N4) |
Do not treat elevated C-reactive protein (CRP) or procalcitonin levels in serum with antibiotics in patients not presenting signs or symptoms of infection (N5)

Secondary outcome measures for the inpatient sector were rate of sepsis therapy in compliance with guidelines (in compliance with the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock, defined as adherence to the 3-hour and 6-hour sepsis bundles [9]); rate of Acute Respiratory Distress Syndrome (ARDS) therapy in compliance with guidelines (measured against the evident ventilation targets, ventilation with low ventilation volumes and low peak pressures: with controlled ventilation: breath volume of 6 ml/kg calculated ideal body weight, positive end-expiratory pressure (PEEP) setting in proportion with the necessary FiO2, plateau pressure < 30 cm H2O, [26]); ICU and sepsis-related mortality, hospital mortality, ICU length of stay (LOS) and hospital LOS, rate of patients with dialysis at discharge from the ICU; and rate of transfer transport (defined as rate of patients discharged to another hospital).

Secondary outcome measures for the inpatient sector were health related quality of life (measured with the SF-36 v2.0 questionnaire).

In our protocol the three process variables "Rate of sepsis diagnosis" and "Rate of ARDS diagnosis" and “Rate of undiagnosed sepsis” were listed as part of the secondary outcomes. We corrected this in the report. All process variables are now reported as such.

Randomization and masking

Participating hospitals and outpatient physician offices were randomly assigned to four clusters of 4-5 hospitals and four clusters of 23-28 outpatient physicians’ offices (Multimedia appendix 1: Study schedule using a stepped-wedge design (inpatient sector), and Multimedia appendix 2: Study schedule using a stepped-wedge design (outpatient sector). Participants were randomly assigned to one of the clusters with different start dates for the intervention phase by an independent statistician using a computer-generated random allocation sequence. It was not possible to mask the healthcare staff or patients, as they were involved in the delivery of the intervention.

Statistical methods

Primary outcomes were evaluated using binary logistic regression models (primary data) and zero-or-one inflated beta regression models (AHIP data).

In the analyses of the inpatient data, we controlled for the treating hospital, patient age and the Sequential Organ Failure Assessment (SOFA) score at enrolment in the study [27]. SOFA scores were calculated based on the data in routine clinical patient records. Missing baseline values for the different SOFA sub-scores were imputed, if available, by measurements within the first three days after enrolment (next observation carried backward) [28]. Only patients with complete SOFA scores (i.e., measurements for all six sub-scores) at baseline were included in the analyses.

To differentiate the training effect and the external effect of expert teleconsultations from the direct counselling effect, the intervention group was separated into patients with and without expert teleconsultations, as not all patients who received interventions were treated with expert teleconsultations. Models for ICU and sepsis-related mortality and sepsis bundle compliance were specified in the same manner. Effects on the LOS were estimated using a linear, a gamma and a log-linear regression model with the same control variables.

In the evaluation of the primary outpatient data, we controlled for the treating outpatient physician and patient age. Three different models were estimated for each outcome:
- Model 1 contained only the group variable (group) and the control variables.
- Additionally, model 2 contained a count variable (n) that recorded the number of expert teleconsultations the outpatient physician had already used before the visit with the respective patient.
- Additionally, model 3 contained a quadratic term of the count variable (n^2) to map possible learning curves among outpatient physicians in the sense of a decreasing marginal utility of the expert teleconsultations.

In the AHIP data, influenza and measles vaccination rates were documented quarterly at the practitioner level. To isolate the effect of the intervention on the vaccination rates, we controlled for the treating practitioner, the number of patients during the quarter and seasonal/quarterly effects. Baseline group differences were tested using odds ratios for binary variables or t-tests for metric variables. Data cleaning and statistical analyses were performed in R (version 3.6.3) using the functions glm for logistic models and gamlss for beta regression models. Confidence intervals for regression estimates were computed using the confint command from the stats package, which calculated the confidence intervals (CI) based on profile likelihood estimation. All analyses were based on a significance level of alpha=5%. The model structures are detailed in the Multimedia appendix 4: Model structures.

Results
Seventeen hospitals and 103 outpatient physicians underwent randomisation. The participating hospitals had between 101 and 449 beds; participating ICUs had on average 10 ICU beds (range 5-14) and were mixed medical-surgical ICUs staffed with anaesthesiologists and internists. Hospitals were in both urban and rural areas. Eight hospitals served populations < 50,000; seven hospitals served populations from 50,000 to 100,000; and two hospitals served populations > 250,000. Most outpatient physicians were in urban areas with a high outpatient physician density per capita. Among the participating doctors, multiple specialties were represented, and the majority were general practitioners, internists, ophthalmologists, or gynaecologists. Between 3 May 2017 and 30 September 2019, eligible patients (n=159,424) who required infectious disease and/or intensive care treatment were enrolled in our study (Figure 1). Overall, we provided 8,505 inpatient expert teleconsultations. For outpatients, the average teleconsultation rate was 1.33%. In the following, we report first the results of the inpatient and then of the outpatient sector.
Inpatient study enrolment

After initial triage by the attending physicians, we enrolled 10,585 inpatients (Multimedia appendix 5: Study enrolment over time (inpatient sector)). Baseline characteristics of the inpatients are detailed in Table 2. Sixty patients with incomplete data were excluded from the analysis and we provide details on the distribution of missing values before and after imputation (Multimedia appendix 6: Missing value distribution of baseline SOFA-Scores). For the recommendation “Staphylococcus aureus bloodstream infection imperatively needs efficacious antimicrobial treatment and identification and elimination of the source of infection”, the SOFA score was not included in the statistical model, as we mainly observed non-ICU Patients for this outcome, for whom the relevant parameters to calculate the score are not routinely recorded.

Compared with those in the control group, inpatients in the intervention group were older (mean age 69.25 years in the control group versus 72.14 years in the intervention group) and had higher SOFA scores at baseline (mean SOFA 3.58 in the control group versus 4.12 in the intervention group). The higher morbidity in the intervention group also manifested itself in a higher sepsis rate (5% versus 9%) and a higher ARDS rate (13% versus 17.9%). For the outcome-specific analysis samples, we found no fundamental deviations from the characteristics of the overall sample.
## Inpatient primary outcomes

We found significant between-group differences in the management of *Staphylococcus aureus* bloodstream infections (“*Staphylococcus aureus* bloodstream infection imperatively needs efficacious antimicrobial treatment and identification and elimination of the source of infection”, P1). As expert teleconsultations were provided to all patients in this analysis, we did not divide the intervention group to estimate the effects of the intervention on this recommendation. Patients in the intervention group were significantly more likely to be treated in accordance with the recommendation (OR 4.004 [95% CI 1.828, 9.202], P=.001) (Table 3).

The direct effect of expert teleconsultations became also evident in the treatment of critically ill patients with severe sepsis and septic shock. We found significant between-group differences for the recommendation “In critically ill patients with signs of infection, early appropriate antibiotic therapy is crucial after obtaining cultures, and treatment should be regularly re-evaluated” (OR 6.822 [95% CI 1.271, 56.607], P=.04, Table 3). However, intervention patients who did not receive expert teleconsultations also received treatment that was more in line with the guideline recommendation than that received by the control group. Notably, across all included patients diagnosed with severe sepsis and septic shock, adherence to this recommendation was negatively associated with patient age (Table 3).

We found no significant intervention effects for the recommendation “Prescribe oral forms of highly bioavailable antimicrobial agents to patients who can reliably receive and absorb medications via the enteral route” (Table 3).

Regarding the recommendations “Do not treat asymptomatic bacteriuria with antibiotics” (n = 24) and “Do not treat Candida recovered from respiratory or gastrointestinal tract specimens” (n = 32), we had too few observations to generate logistic regression models (Table 3).

Regarding the extension of the period of treatment with prophylactic antibiotics after surgery once a patient has left the operating room, we observed a higher guideline adherence in patients in the intervention group who did not receive expert teleconsultations than in patients in the control group (OR 9.372 [95% CI 1.519, 111.467], P=.04, Table 3). However, the estimated coefficient for the
portion of the intervention group who directly received expert teleconsultations remained statistically nonsignificant. Furthermore, no significant intervention effects could be found for the recommendation “Do not treat elevated C-reactive protein (CRP) or procalcitonin levels in serum with antibiotics in patients not presenting signs or symptoms of infection” (Table 3). It should be noted that the latter was already fulfilled in 90% of the control cases.

Table 3 – Regression analyses of inpatient primary outcomes

|                | P1' (N=186) | P2' (N=211) | P5' (N=126) | N4' (N=193) | N5' (N=919) |
|----------------|-------------|-------------|-------------|-------------|-------------|
|                | Compliance n/N (%) | OR (95% CI) | P value | Compliance n/N (%) | OR (95% CI) | P value | Compliance n/N (%) | OR (95% CI) | P value | Compliance n/N (%) | OR (95% CI) | P value |
| Control variables |             |            |            |             |            |            |             |            |            |             |            |        |
| SOFA score     | 0.973       | 0.92 - 1.064 | .51 | 1.004 - 1.064 | 0.753 - 1.879 | .51 | 0.996 - 1.004 | 0.51 | 2.068 - 0.975 | .03 |
| Age            | 0.001       | 0.992 - 0.993 | .92 | 1.005 - 1.006 | 0.667 - 1.687 | .51 | 0.991 - 1.000 | 0.97 | 1.000 - 1.007 | .97 |
| Group variables |             |            |            |             |            |            |             |            |            |             |            |        |
| Control group  | 75/92       | Ref | 29/59 | Ref | 78/100 | Ref | 110/129 | Ref | 531/590 | Ref |           |
| Intervention group | 43/94 | 4.004 | <.001 | 40/104 | 4.275 | <.001 | 85/135 | 90.0% |              |
| without teleconsultation | 108/132 | 0.001 | 1.000 | 0.600 | 0.99 | 31/33 | 3.172 | 0.03 | 163/192 | 0.990 | 0.97 |
| with teleconsultation | 61/32 | 0.000 | (1.563, 9.022) | 0.000 | (1.032, 0.542) | (0.59, 11.467) | 0.04 | 34/84 | (0.542, 1.834) |              |
|                | 90.0% | (1.271, 7.483) | (0.009, 25.0%) | 0.017 | (0.001, 7.483) | (0.001, 25.0%) | 0.017 | 90.0% | (0.001, 7.483) | (0.001, 25.0%) | 0.017 |

- not applicable; CI confidence interval; OR odds ratio; Ref reference group; Each model also controlled for hospital specific effects, which are not reported individually in this table; CIs were calculated based on profile likelihood estimation.

Primary Outcomes:
* P1' Imperatively start antimicrobial treatment and remove the focus on Staphylococcus aureus bloodstream infection.
* P2' Critically ill patients with signs of infection need early appropriate antibiotic therapy.
* P5' Prefer oral formulations of highly bioavailable antimicrobials whenever possible.
* N4' Do not prolong prophylactic administration of antibiotics in patients after they have left the operating room.
* N5' Do not treat an elevated C-reactive protein (CRP) or procalcitonin level with antibiotics in patients without signs of infection.

Inpatient secondary outcomes

Significant between-group differences were also found in the adherence to the 3-hour and 6-hour sepsis bundles for patients with the diagnoses of severe sepsis and septic shock (Figure 2 and Multimedia appendix 8: Regression analyses of sepsis bundle compliance). Overall (0-6 hours), patients in the intervention group with expert teleconsultations outperformed the controls with regard to sepsis bundle compliance (OR 7.739 [2.379, 28.026], P=.001). This was mainly driven by an improvement in compliance with the 4-6 hour bundle. With expert teleconsultations, the odds of being treated in accordance with the guideline recommendations in the 4-6 hour therapy course after receiving a diagnosis of sepsis were 14.2-times higher (OR 14.245 [95% CI 3.121, 85.424], P=.001) than in the control group. Overall and for the 3- and 6-hour sepsis bundles, we found significant improvements in compliance for intervention patients who did not receive direct telemedical treatment support.
Regarding treatment quality in patients with mild ARDS, the descriptive analysis showed an increase in compliance from 7.4 % (16/217) in the control group to 18.4 % (9/49) in the intervention group without expert teleconsultations and 11.8 % (19/161) in the group with expert teleconsultations. In the logistic regression model, a significant OR of 3.621 [95% CI 1.256 - 10.319], P=.02) was obtained for patients without expert teleconsultations. Patients with expert teleconsultations also showed a significantly increased chance of correct treatment mild ARDS (OR 2.355 [95% CI 1.023 - 5.516], P=.04). For patients with moderate or severe ARDS we could not demonstrate these effects. A detailed description of this outcome is presented as Multimedia appendix 7: Regression analysis of ARDS therapy compliance.

Regarding ICU mortality (OR 1.276 [95% CI 0.909, 1.794], P=.16) and sepsis-related mortality (OR 0.680 [95% CI 0.230, 1.0874], P=.37), no statistically significant intervention effects were found in our model estimations; however, a reduction in the sepsis-related mortality rate of 5% was achieved (28.8% (19/66) in the control group versus 23.8% (50/210) in the intervention group). Also, no significant improvements with regard to hospital mortality were observed.

ICU LOS was significantly longer for intervention patients with (+1.971 days [95% CI 1.858, 27.708], P=.004) and without (+2.253 days [95% CI 2.235, 40.535], P=.002) expert teleconsultations than for the respective controls. Regarding hospital length of stay, it is noticeable that patients in the control group were hospitalised longer (mean 16.3 days, 95% CI 15.65 - 16.97 days) compared to patients in the intervention group without expert teleconsultations (mean: 14.15 days; 95% CI 12.96 - 15.35 days) but for shorter periods than patients with expert teleconsultations (mean: 20.62 days; 95% CI 19.55 - 21.70 days). The linear regression model confirms this result for patients with expert teleconsultations.
teleconsultations. These patients stayed on average 4.6 days (β: 4.610 days; 95% CI 3.316 - 5.905 days; P<.001) longer in hospital than control patients. For the group of patients without expert teleconsultations there was no significant difference to the control group.

Six (0.3%) patients in the control group and eight (1.1%) in the intervention group were discharged from hospital on dialysis. With this very low prevalence, effects of any intervention cannot be shown.

Overall, 4.4% (86/1,965) of the control group patients were transferred to another hospital during our study. In the intervention group, this proportion was 11.3 % (143/1,261). Patients with expert teleconsultations were transferred more frequently (11.8%; 101/857) than intervention patients without expert teleconsultations (10.4%; 42/404). The model calculation also shows a significant intervention effect. Patients who received an expert teleconsultation had a 2.9-fold higher chance of being transferred (OR: 2.903; 95% AI: 2.012 - 4.186; P<.001). In intervention patients without expert teleconsultations, this chance was also significantly increased compared to the control group (OR: 2.432; 95% CI: 1.570 - 3.721). Overall, the analyses thus show an increase in the number of transfers due to the intervention.

**Outpatient study enrolment**

In the outpatient sector, 148,839 patients were enrolled in our study. The intervention group differed significantly from the control group with regard to their distribution between the two physician networks. Baseline characteristics are detailed in Table 4, and Multimedia appendix 9: Study enrolment over time (outpatient sector) provides details concerning study enrolment.

### Table 4 – Outpatient characteristics

|                      | Control group | Transition group | Intervention group |
|----------------------|---------------|------------------|--------------------|
|                      | Mean/n (%)    | Mean/n (%)       | Diff (95% CI) a    | P-value        |
| **Outpatient characteristics** |               |                  |                   |                |
| Number of patients   | 47,250        | 67,650           | 33,939             | -              |
| (54.8%)              | (54.6%)       | (54.8%)          |                   |                |
| Age (years)          | 42.08         | 40.50            | 42.20              | 0.12           | .49            |
| (45.2%)              | (45.4%)       | (45.2%)          | (-0.4538, 0.2208) |                |                |
| Sex                  |               |                  |                    |                |
| Male                 | 25,908        | 36,962           | 18,584             | -              | .83            |
| (54.8%)              | (54.6%)       | (54.8%)          |                   |                |
| Female               | 21,342        | 30,688           | 15,355             | -              | .83            |
| (45.2%)              | (45.4%)       | (45.2%)          |                   |                |
| Physician network    |               |                  |                    |                |
| MuM                  | 31,248        | 43,412           | 21,388             | -              | <.001          |
| (66.1%)              | (64.2%)       | (63.0%)          |                   |                |
| GKS                  | 16,002        | 24,238           | 12,551             | -              | <.001          |
| (33.9%)              | (35.8%)       | (37.0%)          |                   |                |
- not applicable; a Diff means difference vs. control group

**Outpatient primary outcomes**

Use of expert teleconsultation was associated with a significantly higher degree of adherence to the
guideline recommendations for antibiotic therapy. Overall, the treatment of patients in the intervention group was significantly more compliant than that in the control group with regard to the Choosing Wisely® recommendation for the treatment of uncomplicated upper respiratory tract infections (N1; OR 1.343 [95% CI 1.155, 1.562], P=.001; model 1). This effect was significantly influenced by the number of expert teleconsultations conducted, as indicated by the estimated coefficient of the count variable (OR 1.007 [95% CI 1.001, 1.013], P=.04; model 2). In addition, the estimated coefficient for the quadratic term of the count variable showed a statistically significant negative effect, which illustrates the decreasing marginal utility of the expert teleconsultations (OR 0.9998 [95% CI 0.9996, 0.9999], P=.001; model 3). Here, we also observed an accumulation of noncompliance in the treatment of older patients (Table 4).

Our telemedical inpatient-outpatient network also achieved significant results with regard to the management of asymptomatic bacteriuria (N2). Patients in the intervention group were more likely to be treated in line with the guideline recommendations than were the controls (OR 9.312 [95% CI 3.794, 25.936], P<.001; model 1). This effect was influenced more by the number of expert teleconsultations conducted than by the training of the treating physicians (OR 1.533 [95% CI 1.212 – 2.190], P=.004; model 2). Although not statistically significant, we also observed a trend towards a decreasing marginal utility of the expert teleconsultations with regard to this outcome (model 3). The Choosing Wisely® recommendations also provide advice for increasing influenza (P3) and measles vaccinations (P4). For these analyses, we examined the quarterly vaccination rates at the physician level during the study period. In our basic model, we found no significant effect of expert teleconsultations on influenza vaccinations (rate ratio (RR) 1.089 [95% CI 0.911, 1.302], P=.34). However, to better capture seasonal effects on the vaccination rates, we additionally constructed a model in which we extended the observation period and considered the transition phase as part of the intervention phase because the expert training occurred at the end of the control phase. In this model, intervention physicians had significantly higher influenza vaccination rates (RR 1.204 [95% CI 1.079, 1.344], P=.001). Regarding measles vaccination rates, we found no significant intervention effects in either model.

Table 5 – Regression analyses of outpatient primary outcomes

|                         | Model 1 | Model 2 | Model 3 |
|-------------------------|---------|---------|---------|
|                         | Compliance n/N (%) | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| **N1 (N=15,714)**      |         |         |         |
| Age                    | -       | 0.978   | <.0001  | 0.978       | <.0001  | 0.978       | <.001  |
| Control group          | 7,006/9,456 (80.4%) | 0.975 (0.975, 0.980) | <.0001 |
| Intervention group     | 5,643/6,258 (90.2%) | 1.343 (1.155, 1.562) | 0.001  | 1.198       | (0.997, 1.438) | .0528  | 0.999       | .99    |
| Number of teleconsultations | 1,007 (1,001, 1,013) | .0351 &<.001 | 1.032  | .0100       | (0.806, 1.238) | .001   |
| Squared number of teleconsultations | 0.000 (0.000, 0.999) | .0001 |
| **N2 (N=752)**         |         |         |         |
| Age                    | -       | 0.996   | .5534   | 0.999       | .8306   | 0.999       | .84    |
| Control group          | 145/266 (54.5%) | 0.981 (0.981, 1.010) | .0124  | 0.985       | (0.985, 1.012) | .0124  |
| Intervention group     | 369/486 (75.9%) | 0.932 (0.794, 25.936) | .0617  | 0.147       | (0.040, 2.121) | .066   | 0.092       | 16     |
| Number of teleconsultations | 1,533 (1,212, 2,190) | .0038 &0.88 | 1.171  | .819        | (0.819, 3.174) | .85    |
| Squared number of teleconsultations | 0.000 (0.000, 0.978) | .1038 |

* not applicable; CI confidence interval; OR odds ratio; Ref reference group; Each model also controlled for physician-specific effects, which are not reported individually in this table; CIs were calculated based on profile likelihood estimation.

Primary outcomes:
*N1 Avoid prescribing antibiotics for uncomplicated upper respiratory tract infections,
*N2 Do not treat asymptomatic bacteriuria with antibiotics.

Outpatient secondary outcome
We had planned to assess health related quality of life in outpatients measured with the SF-36 v2.0 questionnaire. Completed questionnaires from a total of 540 patients were available for the initial survey time t0 (study enrolment). This corresponds to 0.4 % of the 148,839 patients included in the outpatient study. 72 (13.3 %) of the 540 patients were eligible for a further survey after 3 or 12 months, as the contact data required for a renewed contact were collected for them at t0. The response rates in the follow-ups for these 72 patients were 31.9% (23/72) for t1 and 27.8% (20/72) for t2. An analysis of changes over time did not appear to be appropriate based on the low response rates for t1 and t2, and no analysis was performed.

Discussion

Summary of main findings

To the best of our knowledge, TELnet@NRW is the largest telemedical cluster randomized controlled study in Europe, with more than 150,000 patients. We established a telemedical inpatient-outpatient network as a novel digital structure in the healthcare system, and we found that it measurably improved the quality of patient care. The consistent introduction and implementation of standardised communication using a certified electronic patient record was a feature that was essential for increasing the effectiveness of the processes involving the new digital health network. The key findings of this study suggest that expert teleconsultation is an effective tool to provide inpatient and outpatient physicians with evidence-based expertise on a large scale, thus improving guideline compliance and the quality of infectious disease and intensive care management. Concerning the inpatient primary outcomes, our telemedical intervention had significant quality-improving effects on the management of *Staphylococcus aureus* bloodstream infections (P1), severe sepsis and septic shock (P2) and prophylactic antibiotic therapy (N4). Quality improvements for several outcomes reached not only those patients who were treated with direct expert teleconsultations but also other patients treated by the same physicians. This finding can be interpreted as a positive effect of the initial training courses and/or an indirect effect of the expert teleconsultations. It can therefore be assumed that the treating physicians also apply the knowledge acquired in teleconsultations to patients whose treatment is carried out without telemedical support.

In the outpatient sector, our telemedical intervention significantly increased guideline compliance in the management of uncomplicated upper respiratory tract infections (N1) and asymptomatic bacteriuria (N2). The chance of being treated according to the recommendations was positively associated with the number of teleconsultations already participated in by the outpatient physician prior to the respective patient visit. Furthermore, we found evidence for a decreasing marginal utility of these teleconsultations, which may reflect the physicians’ learning curve. To obtain a better understanding of physicians’ learning behaviour and the associated practical implications, studies with longer observational periods are needed. Basic analyses of influenza and measles vaccination rates uncovered no significant intervention effects. However, when considering the initial transition phase as part of the intervention phase, influenza vaccination in the intervention group increased significantly. This could be explained either by the better statistical control of seasonal effects (as more observation quarters were included) or by the fact that the effects were larger immediately after the start of the intervention. The latter would indicate that the transition period was probably too long to capture the full potential of our intervention. Nevertheless, since this analysis deviates from the original study plan, it can only be interpreted as exploratory.

With regard to our secondary outcomes analysed for the inpatient sector, we found that the provision of expert teleconsultations led to a higher overall sepsis bundle adherence, which was mainly driven by improvements in compliance with the 4-6 hour bundle. However, although the direct relationship between sepsis bundle compliance as a quality of care indicator and mortality is well documented in...
the scientific literature [10-15,20,29], we did not observe significant intervention effects on ICU mortality, sepsis-related mortality or hospital mortality. Although its cross-sectoral applicability was one argument for selecting compliance with the Choosing Wisely® recommendations as the primary outcome of this study, parts of these recommendations are not applicable to both inpatient and outpatient care, especially the ICU setting. Since gastrointestinal function is very often impaired in ICU patients and therefore the absorption of oral medications cannot be guaranteed, most medication is administered intravenously. Likewise, obtaining tracheal secretions and microbiological tests is a rarity in the outpatient sector, as the therapeutic consequence outside of serious infections is very low. Since the majority of ICU patients have an indwelling urinary catheter and/or are sedated, the criterion "asymptomatic" cannot be evaluated in the context of bacteriuria. Notably, the compliance with abstaining from treating elevated C-reactive protein (CRP) or procalcitonin levels in the serum with antibiotics in patients without signs or symptoms of infection was already 90% in the control phase. In summary, 4 out of 10 Choosing Wisely® recommendations for infectious disease management are not fully applicable to ICU care.

Within the real world setting of our trial, it was at the discretion of the practitioners for which patients an expert teleconsultation was requested. Hence, attending physicians tended to include patients thought to be more ill during the intervention phase of the study, which is reflected by the higher SOFA scores, sepsis and ARDS incidences for inpatients in the intervention phase compared to the control phase. We controlled for such selection effects by including relevant variables in our regression models, but we could not rule out the presence of unknown confounders for which there were no data available. Although our regression models were adjusted for the SOFA score, this may not have fully controlled for the differences in the baseline risks of morbidity and mortality between the study groups. It is unclear to what extent this problem has been aggravated by the frequent occurrence of missing values for the different SOFA sub-scores and the associated need for data imputation. It should be highlighted that TELnet@NRW was not designed or powered to detect differences in sepsis-related mortality because the primary outcome focused on quality indicators for infectious disease management (Multimedia appendix 3: Analysis algorithms of the 10-Choosing Wisely Recommendations). Nevertheless, in the treatment of septic patients, the early detection of sepsis followed by the early initiation of therapy conforming to the recommendations in the guidelines significantly improves the clinical outcomes [8,10,20,24,30]. Hence, if expert teleconsultations continue to be part of routine health care, we expect that this will also have a positive effect on mortality in intensive care units, as has been reported in similar trials in the past [12, 20, 24]. The equivalent is well documented in the literature regarding adherence to evidence-based management of Staphylococcus aureus bacteraemia. Guideline adherence significantly improves clinical outcomes and reduces mortality [31-35].

As Hemming et al. [22] note, control for secular effects plays a crucial role in stepped-wedge trials. However, especially the need for an appropriately long transition phase to implement the intervention at the participating sites impeded an adequate mapping of time in our statistical models. To address this shortcoming, we estimated secular effects on our inpatient primary outcomes under consideration of transition phase data in a secondary analysis. Our models incorporate time in two ways: (1) the days since the beginning of the study (i.e. the beginning of the control phase) and (2) the days since the beginning of the transition phase. Results of the estimations are displayed in the Multimedia appendix 10: . For most of the primary outcomes we observed no significant time effects (P5, N4, N5). The estimation for P2 shows a significant negative overall time effect (1) and a significant positive effect since beginning of the implementation of the intervention (2). Thus, we conclude that our intervention was a major driver of the observed improvements and that our primary model without time variables may rather tend to underestimate the intervention effects. For outcome P1, however, the estimation shows significant time effects pointing in the opposite direction. It can be assumed that the negative time effect observed since the beginning of the transition phase is
largely due to implementation difficulties in the participating normal wards. However, we cannot rule out that the intervention effects measured in the primary evaluations were overestimated due to a possible time trend.

**Limitations**

Overall, the findings of this study should be interpreted in the context of its limitations. The participating hospitals, ICUs and outpatient physicians were not chosen at random; instead, the 17 sites and 103 outpatient physicians were self-selected based on their willingness to participate in a study to improve patient care. However, we chose a randomised stepped-wedge design to control for clinical characteristics, demographics, and setting to protect our findings against bias. Nevertheless, our results should be interpreted with the consideration of the possibility for selection bias due to the on-site triage of patients. We controlled for such selection effects by including relevant variables in our regression models, but we could not rule out the presence of unknown confounders for which there were no data available. We also acknowledge potential bias related to secular trends in care given the fact that the control and intervention clusters did not overlap in time. Furthermore, for some outcomes, the real effect size remained uncertain, which is reflected by the large CI. This holds true especially for sepsis bundle compliance. Nevertheless, there is sufficient certainty that the associated odds ratios were greater than 1; thus, intervention effects existed.

**Conclusions**

Despite the mentioned limitations, TELnet@NRW robustly demonstrated that a cross-sectoral health network, as a new digital structure in the healthcare system, can develop into a quality network that operates under the premise that cross-sectoral and interregional cooperation can significantly improve evidence-based care. Based on the technical equipment, the principles of TELnet@NRW are transferable from intensive care medicine and infectious disease management to other sub-specialist medical fields that mostly rely on expert knowledge. Thus, the concept of TELnet@NRW can be adapted to other patient populations, other conditions, or other areas, in which expertise rather than equipment needs to be transported over large distances. Our results must also be interpreted in light of the most recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic; a digital inpatient-outpatient health network is well suited to meeting pressing challenges faced by healthcare systems, which we will have to address in the future (e.g., staff shortages in healthcare sectors, lack of experts in the geographical area, and ageing societies). However, further research is needed with regard to the long-term patient-relevant effects of our telemedical solution and its cost-effectiveness especially in less complex cases in the outpatient setting.

**Acknowledgements**

GM, KS, SWL, RD, SD, DB, CJ and AP contributed to the study concept and design. GM, KS, RD, CJ, JE, AG, CL, SWL, MH, FJ-K, SD, DB, HS-S, SR, JK, and AP contributed to data acquisition. WG, DG, SE, and AP conceptualized and performed the statistical analysis. GM, KS, RD, WG, DG, SE, SD, AP and CB contributed to data interpretation. GM, SD, CB, DG, SE and WG wrote the report, with critical revision for important intellectual content by all other co-authors. All authors read and approved the final manuscript. GM supervised the study. We thank all the patients who participated in the study and the clinical and research staff at all the participating sites, without whose assistance the study would never have been completed. We wish to thank all members of the TELnet@NRW study group, who are listed in the Multimedia appendix 11: TELnet@NRW Study Group. We also thank Kassenärztliche Vereinigung Nordrhein and
Kassenärztliche Vereinigung Westfalen Lippe for their support of TELnet@NRW. The funder of the study had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interests

GM is the coordinator of the “S1 Guideline Telemedicine in Intensive Care Medicine” and chairman of the German Society for Telemedicine (DGTelemed). In the past he has given lectures for Philips. GM is Co-Founder of Clinomic GmbH. WG, SE and DG report grants from the Federal Joint Committee (Gemeinsamer Bundesausschuss), during the conduct of the study. The authors declare no other competing interests.

Abbreviations

| Acronym | Definition |
|---------|------------|
| AHIP    | Association of Statutory Health Insurance Physicians |
| AMR     | Antimicrobial resistance |
| ARDS    | Acute Respiratory Distress Syndrome |
| CI      | Confidence interval |
| ICU     | Intensive care unit |
| LOS     | Length of stay |
| OR      | Odds ratio |
| PEEP    | Positive end-expiratory pressure |
| RR      | Rate ratio |
| SOFA    | Sequential Organ Failure Assessment |
| WLAN    | Wireless local area network |

Multimedia Appendix

Multimedia appendix 1: Study schedule using a stepped-wedge design (inpatient sector)
Multimedia appendix 2: Study schedule using a stepped-wedge design (outpatient sector)
Multimedia appendix 3: Analysis algorithms of the 10-Choosing Wisely Recommendations
Multimedia appendix 4: Model structures
Multimedia appendix 5: Study enrolment over time (inpatient sector)
Multimedia appendix 6: Missing value distribution of baseline SOFA-Scores
Multimedia appendix 7: Regression analysis of ARDS therapy compliance
Multimedia appendix 8: Regression analyses of sepsis bundle compliance
Multimedia appendix 9: Study enrolment over time (outpatient sector)
Multimedia appendix 10: Regression analyses of secular effects on inpatient primary outcomes
Multimedia appendix 11: TELnet@NRW Study Group
References

1. World Health Organization. Global strategy on human resources for health: Workforce 2030. 2016. http://apps.who.int/iris/bitstream/handle/10665/250368/9789241511131-eng.pdf;jsessionid=B1755A0460481610D2ECEC76330181B2?sequence=1 [accessed Jan 21 2022].

2. European Commission. Commission Staff Working Document on an Action Plan for the EU Health Workforce. 2012. https://op.europa.eu/de/publication-detail/-/publication/402bad92-c66f-4d45-9984-70e199dfd312/language-en [accessed Jan 21 2022].

3. European Commission. Strategic Research Agenda For Robotics in Europe 2014-2020. 2013. https://www.eu-robotics.net/cms/upload/topic_groups/SRA2020_SPARC.pdf [accessed Oct 05 2021].

4. European Commission. Population structure and ageing. 2020. https://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing [accessed Jan 21 2022].

5. O’Neill J. Tackling drug-resistant infections globally: final report and recommendations: UK Department of Health, HM Treasury, and the Foreign and Commonwealth Office. 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [access Jan 21 2022].

6. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kevlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-11. PMID:31954465

7. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193(3):259-72. PMID:26414292

8. SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. Intensive Care Med.
9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637. PMID:23353941

10. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Intensive Care Med. 2014;40(11):1623-33. PMID:25270221

11. Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, et al. The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). Intensive Care Med. 2015;41(9):1620-8. PMID:26109396

12. Deisz R, Rademacher S, Gilger K, Jegen R, Sauerzapfe B, Fitzner C, et al. Additional Telemedicine Rounds as a Successful Performance-Improvement Strategy for Sepsis Management: Observational Multicenter Study. J Med Internet Res. 2019;21(1):e11161. PMID:30664476

13. Wathne JS, Harthug S, Kleppe LKS, Blix HS, Nilsen RM, Charani E, et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrob Resist Infect Control. 2019;8:63. PMID:31011417

14. Dylis A, Boureau AS, Coutant A, Batard E, Javaudin F, Berrut G, et al. Antibiotics prescription and guidelines adherence in elderly: impact of the comorbidities. BMC Geriatr. 2019;19(1):291. PMID:31664914

15. Lehmann C, Berner R, Bogner JR, Cornely OA, de With K, Herold S, et al. The "Choosing Wisely" initiative in infectious diseases. Infection. 2017;45(3):263-8. PMID:28290130

16. Leone M, Ragonnet B, Alonso S, Allaouchiche B, Constantin JM, Jaber S, et al. Variable compliance with clinical practice guidelines identified in a 1-day audit at 66 French adult intensive
care units. Crit Care Med. 2012;40(12):3189-95. PMID:23027124.

17. Brunkhorst FM, Engel C, Ragaller M, Welte T, Rossaint R, Gerlach H, et al. Practice and perception--a nationwide survey of therapy habits in sepsis. Crit Care Med. 2008;36(10):2719-25. PMID:18766100

18. World Health Organization. Fact sheet antimicrobial resistance. 2018. https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance [accessed Jan 21 2022]

19. ABIM Foundation. Choosing Wisely, a special report on the first five years. 2010. https://www.choosingwisely.org/wp-content/uploads/2017/10/Choosing-Wisely-at-Five.pdf [accessed Jan 21 2022].

20. Lilly CM, McLaughlin JM, Zhao H, Baker SP, Cody S, Irwin RS, et al. A multicenter study of ICU telemedicine reengineering of adult critical care. Chest. 2014;145(3):500-7. PMID:24306581

21. Fakultät für Gesundheitswissenschaften, Universität Bielefeld. Telemedizinisches, intersektorales Netzwerk als neue digitale Gesundheitsstruktur zur messbaren Verbesserung der wohnortnahen Versorgung: Evaluationsdesign. https://www.telnet.nrw/wp-content/uploads/TELnet@NRW_Evaluationsdesign-Analyseplan.pdf [accessed Jan 21 2022].

22. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. J Med Internet Res 2011;13(4):e126. URL: http://www.jmir.org/2011/4/e126/ [accessed Jan 21 2022].

23. German Society for Anesthesiology & Intensive Care Medicine. Telemedicine in Intensive Care Medicine. https://www.awmf.org/leitlinien/detail/ll/001-034.html [accessed Jan 21 2022].

24. Lilly CM, Cody S, Zhao H, Landry K, Baker SP, McIlwaine J, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA. 2011;305(21):2175-83. PMID:21576622
25. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Jr., Hellmich M, Hopkins S, et al. Staphylococcus aureus bloodstream infection: a pooled analysis of five prospective, observational studies. J Infect. 2014;68(3):242-51. PMID:24247070

26. Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin. S3-Leitlinie Invasive Beatmung und Einsatz extrakorporaler Verfahren bei akuter respiratorischer Insuffizienz. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften eV. 2017. https://www.awmf.org/uploads/tx_szleitlinien/001-021l_S3_Invasive_Beatmung_2017-12.pdf [accessed Jan 21 2022].

27. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10. PMID:8844239

28. Kenward MG, Molenberghs G. Last observation carried forward: a crystal ball? J Biopharm Stat. 2009;19(5):872-88. PMID:20183449

29. Ferrer R, Artigas A, Levy MM, Blanco J, Gonzalez-Diaz G, Garnacho-Montero J, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA. 2008;299(19):2294-303. PMID:18492971

30. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2004;30(4):536-55. PMID:14997291

31. Goto M, Schweizer ML, Vaughan-Sarrazin MS, Perencevich EN, Livorsi DJ, Diekema DJ, et al. Association of Evidence-Based Care Processes With Mortality in Staphylococcus aureus Bacteremia at Veterans Health Administration Hospitals, 2003-2014. JAMA Intern Med. 2017;177(10):1489-97. PMID:28873140

32. Perez-Rodriguez MT, Sousa A, Lopez-Cortes LE, Martinez-Lamas L, Val N, Baroja A, et al.
Moving beyond unsolicited consultation: additional impact of a structured intervention on mortality in Staphylococcus aureus bacteremia. J Antimicrob Chemother. 2019;74(4):1101-7. PMID:30689894

33. Lopez-Cortes LE, Del Toro MD, Galvez-Acebal J, Bereciartua-Bastarrica E, Farinas MC, Sanz-Franco M, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of Staphylococcus aureus bacteremia. Clin Infect Dis. 2013;57(9):1225-33. PMID:23929889

34. Nagao M, Yamamoto M, Matsumura Y, Yokota I, Takakura S, Teramukai S, et al. Complete adherence to evidence-based quality-of-care indicators for Staphylococcus aureus bacteremia resulted in better prognosis. Infection. 2017;45(1):83-91. PMID:27709434

35. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012;25(2):362-86. PMID:22491776
Supplementary Files
Figures
Study flow diagram.

17 hospitals and 103 outpatient physicians randomised

Cluster 1: 4 hospitals, 27 outpatient physicians
Cluster 2: 5 hospitals, 25 outpatient physicians
Cluster 3: 4 hospitals, 28 outpatient physicians
Cluster 4: 4 hospitals, 23 outpatient physicians

159,424 patients enrolled

17 Hospitals:
10,585 inpatients enrolled

95 outpatient physicians contributed data:
148,839 outpatients enrolled

60 with incomplete data (e.g., start date)

Timing of enrolment:
4,099 patients during control phase
3,575 patients during transition phase
2,851 patients during intervention phase

Timing of enrolment:
47,250 patients during control phase
67,650 patients during transition phase
33,939 patients during intervention phase

1,538 intervention patients with expert teleconsultations
1,313 intervention patients without expert teleconsultation
5,806 intervention patients treated by practitioners before their first expert teleconsultation
28,133 intervention patients treated by practitioners after their first expert teleconsultation
Sepsis bundle compliance over time.
Multimedia Appendixes
Study schedule using a stepped-wedge design (inpatient sector).
URL: http://asset.jmir.pub/assets/fe06ed2af123b50ecaa12f3638e64a95.docx

Study schedule using a stepped-wedge design (outpatient sector).
URL: http://asset.jmir.pub/assets/3b95f474a7e743108225e2c59354be6d.docx

Analysis algorithms of the 10-Choosing Wisely Recommendations.
URL: http://asset.jmir.pub/assets/72df2d8b4eb96cf7c7001885e07f957c.docx

Model structures.
URL: http://asset.jmir.pub/assets/d38e245d71b1d0b249ad621512f0b.docx

Study enrolment over time (inpatient sector).
URL: http://asset.jmir.pub/assets/2e2c00485dc398c9f7d6b5200ad9dea3.docx

Missing value distribution of baseline SOFA scores.
URL: http://asset.jmir.pub/assets/b9b62040893e72af8e12be99d1e78.docx

Regression analysis of ARDS therapy compliance.
URL: http://asset.jmir.pub/assets/10a89b048a10de86d9a44380ec8a7440.docx

Regression analyses of sepsis bundle compliance.
URL: http://asset.jmir.pub/assets/ac88ade56076f764a8a92ed6a1a2f28.docx

Study enrolment over time (outpatient sector).
URL: http://asset.jmir.pub/assets/5e70d76cd7455f39a96329c92a241a52.docx

Regression analyses of secular effects on inpatient primary outcomes.
URL: http://asset.jmir.pub/assets/9a69cbccd4fd0f6025765085bb0a9848.docx

TELnet@NRW Study Group.
URL: http://asset.jmir.pub/assets/275fb8e44bd6a21ce3f263ec94ab74450.docx
CONSORT (or other) checklists

CONSORT-EHEALTH (V 1.6.1).
URL: http://asset.jmir.pub/assets/a06c3c2a7b0fc7e695f276c24c5e714.pdf