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# The time-dependent "cure-death" model investigating two equally important endpoints simultaneously in trials treating high-risk patients with resistant pathogens

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on behalf of the COMBACTE-NET consortium

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A variety of primary endpoints are used in clinical trials treating patients with severe infectious diseases, and existing guidelines do not provide a consistent recommendation. We propose to study simultaneously two primary endpoints, cure and death, in a comprehensive multistate cure-death model as starting point for a treatment comparison. This technique enables us to study the temporal dynamic of the patient-relevant probability to be cured and alive. We describe and compare traditional and innovative methods suitable for a treatment comparison based on this model. Traditional analyses using risk differences focus on one prespecified timepoint only. A restricted logrank-based test of treatment effect is sensitive to ordered categories of responses and integrates information on duration of response. The pseudo-value regression provides a direct regression model for examination of treatment effect via difference in transition probabilities. Applied to a topical real data example and simulation scenarios, we demonstrate advantages and limitations and provide an insight into how these methods can handle different kinds of treatment imbalances. The cure-death model provides a suitable framework to gain a better understanding of how a new treatment influences the time-dynamic cure and death process. This might help the future planning of randomised clinical trials, sample size calculations, and data analyses.

**KEYWORDS**
antimicrobial resistance, competing risks, endpoint choice, multistate models, pseudo-value regression, RCT design

## 1 | INTRODUCTION

Antimicrobial resistance is a growing worldwide problem, and with few innovative drugs making it to the market, there is an urgent need for new drugs to treat such resistant infections.[1, 2] These acute bacterial diseases arising in hospitalised patients include, for example, hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), that may occur when patients have an unmet medical need resulting in a prolonged hospital stay[3] since an appropriate treatment is not yet available.

Our aim is to improve the design of randomised clinical trials (RCTs) to support the development of new antibacterial drugs. Despite its advantages, there are several challenges in conducting an RCT, eg, the outcome definition. A variety of primary endpoints are used in treatment trials dealing with severe infectious diseases, and existing guidelines do not provide a consistent recommendation. The appropriate primary endpoint to be used in trials including hospitalised patients with HAP or VAP is still a subject of debate. Weiss et al[4] provide a systematic review of characteristics of enrolled populations, inclusion/exclusion criteria, and endpoints

  

addressing the efficacy of antimicrobial treatments. The Foundation for the National Institutes of Health states that future studies must determine which outcomes are most important to patients and should incorporate short-term as well as long-term outcomes.[5]

The European Medicines Agency proposes the clinical outcome of a test-of-cure (TOC) visit as an acceptable primary endpoint.[6] However, mortality, suggested as primary endpoint by the Food and Drug Administration,[7] may have a considerable influence on the cure process. When analysing, eg, the probability to be cured over time, mortality as a competing risk should be taken into account, otherwise, the effect can be biased. In HAP and VAP patients, a high underlying baseline mortality within the first 30 days after infection can be assumed, especially in an intensive care unit. Indeed, Harhay et al[8] emphasise that by using a nonmortality clinical endpoint, statistical methods addressing competing risks are needed. Also, many patients die because of their underlying disease and not because of infection. There are cases in which the infection can be considered as cured and the patient dies nevertheless, especially if the focus of the antimicrobrial treatment lies on microbiological cure. Due to multimorbid conditions and severe illnesses, the question of whether the infection is the leading cause of death is highly debatable. Orgeas et al[9] investigated a few years ago the impact of adverse events in intensive care units. In this review, they clearly demonstrate that patients may die from any other pathology than VAP, even after a cure from VAP, since many patients developed more than one adverse event. Furthermore, Doshi[10] criticises the TOC as endpoint and mentions trials in which patients were deemed "cured" by the trial investigator and died on the same day.

Many strategies are proposed in the literature to handle multiple endpoints.[11-13] Röhmel et al[13] discussed an application of two coprimary endpoints when it is sufficient to show that one endpoint is superior and the other one non-inferior compared to a control. For serious illnesses, it is strongly recommended that a composite endpoint should include both mortality and a clinical endpoint.[5,14,15] However, construction of such an endpoint is challenging and interpretation can be misleading especially when the intervention appears to affect individual outcomes differently.[16] Thus, up to now, most trials focus on cure or death as endpoint to be analysed separately.

There are few examples in this field combining mortality as well as a clinical endpoint. Pocock et al[17] have suggested the win ratio as a new effect measure where pairs of patients from the innovative and control treatment are grouped into winners and losers on the basis of whether the most/least favourable event was experienced first. The win ratio is then calculated as the total number of winner pairs divided by the total number of loser pairs. Evans et al[18] recently proposed a similar design using superiority considerations combined with the desirability of outcome ranking and a response adjusted for the duration of antibiotic risk. A composite score is designed, tailored to compare strategies of antibiotic use by weighting its benefits and potential harms at an individual level. The ranked ordinal clinical outcome is categorised into clinical benefit, clinical benefit with some adverse events, survival without clinical benefit, survival without clinical benefit but adverse events, and death.

We propose to study cure and death as primary endpoints simultaneously in a comprehensive multistate cure-death model as starting point for a treatment comparison of two antimicrobial therapies. The cure-death model is appropriate to examine the whole time-dynamic process summarised by the probability to be cured and alive. In particular, it allows for the fact that patients might die from an underlying illness to which the infection may or may not contribute, either before or after clinical or microbiological cure. Moreover, antimicrobial treatment effects are often apparent early during therapy[5] and can be examined with the help of this model. This multistate model is known as illness-death model and often used in oncology[19] to simultaneously analyse recurrence and death including death as a competing event.

On the basis of an illness-death model, Temkin[20] proposed the "probability-of-being-in-response function" as a useful measure for assessing the response to a treatment (tumour shrinkage) and death in cancer patients. Pepe et al[21] used this model to estimate the prevalence of a transient condition. Such multistate models are appropriate to take account of the time dependency, and well-established statistical methodology is available to adequately analyse multistate data.[22] Ignoring competing risks though may cause misleading and flawed results.[23-29]

Non–inferiority designs are widely used in clinical trials of anti-infective drugs[30] comparing test and control cure proportion at a prespecified timepoint. Starting with this traditional approach, the manuscript is organised as follows: In Section 2.1, we will compare it to an approach based on the proportions of patients cured and alive. In Section 2.2, we will provide an introduction to a test technique based on logrank tests as in Hsieh et al[31] for inferences on treatment effects over a whole time frame and not only at one timepoint. A restricted version of the test technique is presented that is sensitive to a prolonged time to death and duration of cure and a shorter time to cure of the new treatment. The cure-death model enables us to examine the temporal dynamics of the probability to be cured and alive and the probability to die. In Section 2.3, we will introduce the Aalen-Johansen estimator and the pseudo-value regression technique. Originally, regression for multistate models is based on hazard rates that lead to very complex functions for the effect of covariates in advanced multistate settings. Typically, in simple situations, the Cox model[32] is used for a survival setting and

the Fine & Gray model[33, 34] for a competing risks setting. Pseudo-value regression, proposed by Andersen et al[35] and Andersen and Klein,[36] provides an alternative technique to directly model the transition probability to be cured and alive and to test for treatment difference.[37, 38] We will highlight advantages, point out disadvantages, and give a recommendation for a combined approach of these possibilities for a treatment comparison. We demonstrate that the methodology works well for the recent published ceftobiprole trial[39] in Section 3 in which the new regimen ceftobiprole was compared to the two-drug regimen ceftazidime plus linezolid. Additional simulation scenarios in Section 4 offer insight into how the different techniques based on the cure-death model can handle different treatment scenarios.

## 2 | METHODS

The cure-death model (Figure 1) provides an analysis strategy that includes two primary endpoints simultaneously. The timing of the events cure and death as well as their chronological sequence is modelled with an initial state 0 (randomisation), a cure state 1, and a death state two.

On the basis of this model, we will focus on the following possibilities for a treatment comparison:

1. Risk differences with confidence intervals at a prespecified timepoint
2. Restricted logrank-based test of treatment effect
3. Analysis of transition probabilities using the Aalen-Johansen estimator and subsequent examination of treatment effect using pseudo-value regression techniques

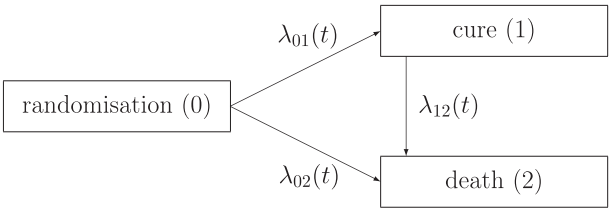


**FIGURE 1** The cure-death model for comparison of two antimicrobial therapies. Let $\lambda_{01}(t)$ be the cure rate, $\lambda_{02}(t)$ the mortality rate without being cured, and $\lambda_{12}(t)$ the rate to die after being cured

### 2.1 | Risk differences

The traditional procedure is to calculate risk differences with corresponding confidence intervals using proportions of cured patients given by

$$\frac{\#\text{cured with treatment A}}{\text{all patients with treatment A}} \quad \text{minus} \quad \frac{\#\text{cured with treatment B}}{\text{all patients with treatment B}}$$

at a prespecified time point for a non–inferiority analysis,[6] as can be seen in Awad et al.[39] We propose to use risk differences with proportions of patients cured and alive given by

$$\frac{\#\text{cured and alive with treatment A}}{\text{all patients with treatment A}} \quad \text{minus} \quad \frac{\#\text{cured and alive with treatment B}}{\text{all patients with treatment B}}$$

that is tantamount with the proportion of patients in state 1 (cure) at this timepoint. A chi-squared test for equality of proportions can be applied.

### 2.2 | Logrank-based test

Hsieh et al[31] propose several tests comparing treatments on the basis of a semi-Markov model. The restricted logrank-based test is a nonparametric method to manage ordered categories of responses and to integrate information on duration of response that fits to the situation present in the cure-death model.

For this, we consider an illness-death process $(X(t), t \in [0, \infty))$ without recovery and state space $S = \{0, 1, 2\}$, with 0 as initial, 1 as cure, and 2 as absorbing death state. We assume that all patients are in the initial state 0 at the start of follow-up, such that $P(X(0) = 0) = 1$ and model the transitions 01, 02, and 12. Analysis of event time data is based on hazards that are represented by the arrows between the states in Figure 1. In this model, the hazards are defined as

$$\begin{aligned}
\lambda_{01}(t) \cdot \mathrm{dt} &= P(X(t + \mathrm{dt}) = 1 | X(t-) = 0), \\
\lambda_{02}(t) \cdot \mathrm{dt} &= P(X(t + \mathrm{dt}) = 2 | X(t-) = 0), \quad \text{and} \\
\lambda_{12}(t) \cdot \mathrm{dt} &= P(X(t + \mathrm{dt}) = 2 | X(t-) = 1).
\end{aligned}$$

They model the instantaneous risk per time unit for the 01, the direct 02, and 12 transition and can be interpreted as the probability that an event happens in the small time interval $\mathrm{dt} = [t, t+\mathrm{dt})$. Proportional cause-specific hazards models can be used to model treatment effects on the transition hazards in the cure-death model. They assume each transition hazard $j \in \{01, 02, 12\}$ to follow a Cox model[32] of the form

$$\lambda_j(t|Z) = \lambda_{0j}(t) \exp(\beta_j' Z),$$

where $\lambda_{0j}(t)$ is the nonnegative baseline hazard function, $\beta_j$ the regression coefficient, and $Z$ the vector of treatment indicators associated with each patient. The partial likelihood, originally introduced by Cox,[40] is used for estimation of the regression coefficients and can be written as

$$\begin{aligned} L(\beta_{01}, \beta_{02}, \beta_{12}) &= L_{01}(\beta_{01}) \\ &\times L_{02}(\beta_{02}) \times L_{12}(\beta_{12}) \\ &= \prod_{k=1}^{K_{01}} \frac{\exp(\beta_{01}' Z_{(k)})}{\sum_{r \in R(t_{01(k)})} \exp(\beta_{01}' Z_r)} \\ &\times \prod_{k=1}^{K_{02}} \frac{\exp(\beta_{02}' Z_{(k)})}{\sum_{r \in R(t_{02(k)})} \exp(\beta_{02}' Z_r)} \\ &\times \prod_{k=1}^{K_{12}} \frac{\exp(\beta_{12}' Z_{(k)})}{\sum_{r \in R(t_{12(k)})} \exp(\beta_{12}' Z_r)}, \end{aligned}$$

where $R(t_{01(k)})$ and $R(t_{02(k)})$ are the sets of individuals that are still in state 0 at transition time $t_{01(k)}$ or $t_{02(k)}$ and at risk for transition 01 or 02, respectively, and $R(t_{12(k)})$ is the set of individuals that are still alive at the transition time to death $t_{12(k)}$. $K_{01}$ is the total number of individuals reaching state cure, $K_{02}$ the total number of individuals reaching state death without being cured, and $K_{12}$ the total number of individuals reaching death after being cured. The likelihood can be factorised for each $j$ so that we can formally analyse each transition separately by treating the others as censored. A test of $\beta_j = 0$, $j \in \{01, 02, 12\}$, is given as a simple score statistic with the score function

$$\left[ \frac{\partial \log L_{01}(\beta_{01})}{\partial \beta_{01}}, \frac{\partial \log L_{02}(\beta_{02})}{\partial \beta_{02}}, \frac{\partial \log L_{12}(\beta_{12})}{\partial \beta_{12}} \right]$$

and the negative expected value of the second derivative of the partial likelihood function as information matrix.

When the data consists of failure time data in two groups, the score test statistic for the Cox partial likelihood is the same as the logrank test statistic since the numerator of the score test for a test of $\beta_j = 0$ turns out to be identical to the numerator, #observed minus #expected, of the logrank test.[41] Moreover, the estimated variance obtained from the Cox model is nearly identical to the denominator in the logrank test.

The logrank test statistic compares estimates of the hazard functions of two (treatment) groups $A$ and $B$ at each time $l$ where there is an event. It is constructed in the following way: For each time $l \in \{1, \ldots, L\}$, let $N_{Al}$ and $N_{Bl}$ be the number of participants at risk and $N_l = N_{Al} + N_{Bl}$. Let $O_{Al}$ and $O_{Bl}$ be the observed number of events in the groups respectively at time $l$, and define $O_l = O_{Al} + O_{Bl}$. Under the null hypothesis of treatment equality and given that $O_l$ events happened at time $l$, $O_{Al}$ is hypergeometrically distributed with parameters $N_l$, $N_{Al}$, and $O_l$. This distribution has expected value $E_{Al} = \frac{O_l}{N_l} N_{Al}$ and variance $V_l = \frac{O_l (N_{Al}/N_l)(1 - N_{Al}/N_l)(N_l - O_l)}{N_l - 1}$. The logrank test statistic compares each observed value $O_{Al}$ to its expectation value $E_{Al}$ under the null hypothesis of equality and is defined as

$$\frac{(O-E)^2}{V} = \frac{\left( \sum_{l=1}^{L} O_{Al} - \sum_{l=1}^{L} E_{Al} \right)^2}{\sum_{l=1}^{L} V_l}.$$

### 2.2.1 | General logrank-based test

Such a test is sensitive to deviations from the null hypothesis of $\beta_j = 0$ of any type. It is constructed by computing the observed and expected number of events ($O$ and $E$) for each transition 01, 02, or 12, in one of the groups at each observed event time and then adding these to obtain an overall summary across all timepoints where there is an event, divided by the variance $V$. The logrank-based (L) test results into the sum of three asymptotically independent logrank test statistics

$$\begin{aligned} \chi_L^2 &= \chi_{01}^2 + \chi_{02}^2 + \chi_{12}^2 \\ &= \frac{(O_{01} - E_{01})^2}{V_{01}} + \frac{(O_{02} - E_{02})^2}{V_{02}} \\ &+ \frac{(O_{12} - E_{12})^2}{V_{12}} \sim \chi^2(3). \end{aligned}$$

### 2.2.2 | Restricted logrank-based test

Yet, the model is not adapted to the request that a transition to cure is preferred over a transition to death. The overall aim is that a patient passes into state 2 (death) as late as possible and remains in state 1 (cure) as long as possible. With a restriction to the regression coefficients in the partial likelihood ($\beta_{01} = -\beta_{12} = -\beta_{02}$), the restricted logrank-based (LR) test statistic respects that ordered response and results in

$$\chi_{RL}^2 = \frac{(O_{RL} - E_{RL})^2}{V_{RL}} \sim \chi^2(1),$$

a test with an embedded structure where $O_{RL} = O_{02} - O_{01} + O_{12}$, $E_{RL} = E_{02} - E_{01} + E_{12}$ and $V_{RL} = V_{02} + V_{01} + V_{12}$. It incorporates all required aspects into one single statistic being $\chi^2$ distributed with one degree of freedom. This restricted version is sensitive to deviations from the null hypothesis if a transition to cure dominates a direct death transition, and if cured, a patient remains in the cure state. Hsieh et al[31] showed that this test statistic achieves the highest power when one treatment is better than the other for all three transitions in the desired way (more patients are cured, less patients die directly, and less patients die after cure).

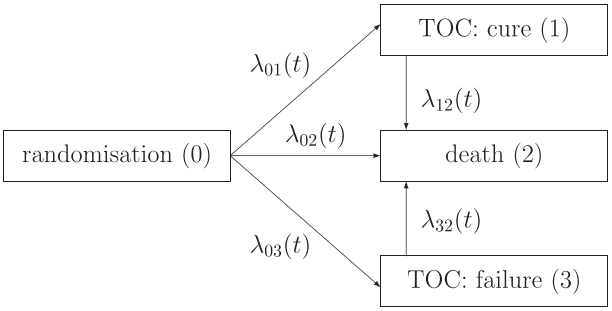


**FIGURE 2** The extended cure-death model for the comparison of two antimicrobial therapies in the ceftobiprole trial.[39] Let $\lambda_{01}(t)$ be the cure rate for cure at the test-of-cure (TOC) visit, $\lambda_{02}(t)$ the mortality rate without being cured at TOC, $\lambda_{03}(t)$ the failure rate for failure at TOC, $\lambda_{12}(t)$ the rate to die after deemed cured at TOC, and $\lambda_{32}(t)$ the rate to die after deemed as a failure at TOC

These tests can easily be extended if an additional state needs to be included as in Section 3 (see Figure 2) as

$$\begin{aligned}\chi^2_L &= \chi^2_{01} + \chi^2_{02} + \chi^2_{12} + \chi^2_{03} + \chi^2_{32} \\ &= \frac{(O_{01} - E_{01})^2}{V_{01}} + \frac{(O_{02} - E_{02})^2}{V_{02}} + \frac{(O_{12} - E_{12})^2}{V_{12}} \\ &\quad + \frac{(O_{03} - E_{03})^2}{V_{03}} + \frac{(O_{32} - E_{32})^2}{V_{32}} \sim \chi^2(5)\end{aligned}$$

and

$$\chi^2_{RL} = \frac{(O_{RL} - E_{RL})^2}{V_{RL}} \sim \chi^2(1),$$

where $O_{RL} = O_{02} - O_{01} + O_{12} + O_{03} + O_{32}$, $E_{RL} = E_{02} - E_{01} + E_{12} + E_{03} + E_{32}$ and $V_{RL} = V_{02} + V_{01} + V_{12} + V_{03} + V_{32}$.

## 2.3 | Transition probabilities and pseudo-value regression

We propose to investigate the probability to be cured and alive and the probability to die over the whole time frame. Let

$$W = \underset{t}{\text{argmin}}(X(t) \neq 0)$$

denote the exit time from the initial state and

$$T = \underset{t}{\text{argmin}}(X(t) = 2)$$

the entry time to the absorbing death state. We have $W = T$ if the process makes a direct 02 transition and $W \leqslant T$ otherwise. The matrix of transition probabilities of a Markov process with state space $S$ is defined as

$$P(s,t) = (P_{kl}(s,t))_{k,l}, \quad k,l \in S$$

with transition probabilities

$$P_{kl}(s,t) = P(X(t) = l | X(s) = k), \quad s \leqslant t.$$

We are especially interested into the probability to be cured and alive, that is, the transition probability

$$\begin{aligned}P_{01}(0,t) &= P(X(t) = 1 | X(0) = 0) \\ &= P(W \leqslant t, t < T) \\ &= \int_0^t P_{00}(0,u)\lambda_{01}(u)P_{11}(u,t)du,\end{aligned}$$

with

$$\begin{aligned}P_{00}(0,t) &= P(X(t) = 0 | X(0) = 0) \\ &= \exp\left(-\int_0^t \lambda_{01}(u) + \lambda_{02}(u)du\right)\end{aligned}$$

and

$$\begin{aligned}P_{11}(s,t) &= P(X(t) = 1 | X(s) = 1) \\ &= \exp\left(-\int_s^t \lambda_{12}(v)dv\right).\end{aligned}$$

Note that $P_{01}(0,t)$ is the same as the state occupation probability $P(X(t) = 1)$ since the initial distribution is degenerate in state 0, that is, $P(X(0) = 0) = 1$.

Let $C$ denote the end of follow-up (right-censored), so that instead of $T$, we observe only $\widetilde{T} = \min(T, C)$. The probability to be cured and alive can be examined using the Aalen-Johansen estimator[42] whereas the probability to die is given by 1 minus the well-known Kaplan-Meier estimator[43] for a simple survival setting. We used the software R with the R package `survival` and `etm`[44, 45] for estimation.

Pseudo-value regression was proposed by Andersen et al[35] and Andersen and Klein[36] and enables a direct regression model for the transition probabilities. With a treatment indicator as covariate, a test of treatment difference can be performed. The idea is to obtain pseudo-values from a jackknife statistic constructed from the Aalen-Johansen estimator that are further used as outcome variables in a generalised linear model.

We begin with selecting a set of $K$ timepoints $s_k$, $k \in \{1, \ldots, K\}$, on which we want to perform regression. The pseudo-values for every patient $i$, $i \in \{1, \ldots, N\}$, and every timepoint $k$ are computed as

$$\hat{\theta}_i(s_k) = N \cdot \widehat{P}_{01}(0, s_k) - (N-1) \cdot \widehat{P}^{(-i)}_{01}(0, s_k), i \in \{1, \ldots, N\},$$

where $\widehat{P}_{01}$ is the estimated transition probability using the complete sample and $\widehat{P}^{(-i)}_{01}$ the one based on the sample without the $i$th observation. To continue, a consistent estimator of the transition probability is needed, provided by the Aalen-Johansen estimator. The pseudo-values $\widehat{\theta}_i = (\widehat{\theta}_i(s_1), \ldots, \widehat{\theta}_i(s_k))$ can be seen as the contribution of subject $i$ to the estimate of interest. We then use a generalised linear model

$$\log(\theta_i | Z_i) = \beta' Z_{ik},$$

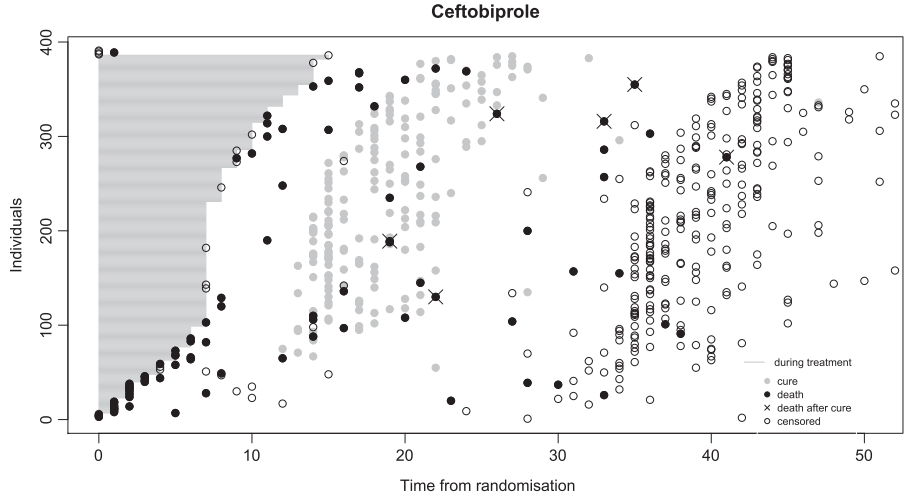


**FIGURE 3** Data visualisation for the ceftobiprole group from a double-blind, randomised, and multicentre trial of patients with HAP/VAP treated with ceftobiprole or ceftazidime plus linezolid.[39] On the x-axis, time from randomisation, which equals time from treatment, is displayed. Cure at TOC is displayed in the form of grey-filled dots after the grey lines describing the time on treatment. The black-filled dots represent death cases, and patients dying after cure are marked with a cross. Censoring can be seen via unfilled dots. HAP, hospital-acquired pneumonia; TOC, test-of-cure; VAP, ventilator-associated pneumonia

with log link function.[46] Finally, we estimate the regression parameters using a generalised estimating equation

$$U(\beta) = \sum_i \left( \frac{dg^{-1}(\beta' Z_{ik})}{d\beta} \right) W_i \left( \hat{\theta}_i - g^{-1}(\beta' Z_{ik}) \right),$$

with identity matrix for the working covariance matrix $W_i$. For estimation, we used the software R, especially the R package `geepack`.[47] $\exp(\hat{\beta})$ can be interpreted as a cure risk ratio (*CRR*) and tests for non–inferiority analyses can be based on the hypotheses

$$H_0 : \quad CRR \leqslant CRR_{ni} \quad \text{versus} \quad H_1 : \quad CRR > CRR_{ni}.$$

Here, $CRR_{ni}$ is the non–inferiority margin.

## 3 | APPLICATION TO THE CEFTOBIPROLE TRIAL

The cure-death model provides a suitable framework for analysing the data of the recently published ceftobiprole trial.[39] The new regimen ceftobiprole was compared with the 2-drug regimen ceftazidime plus linezolid in a double-blind, randomised, multicentre trial in 781 patients with HAP, amongst them 210 with VAP. Ceftobiprole belongs to the class of $\beta$-lactam antibiotics and was established to combat a wide range of gram-positive bacteria, such as, eg, *Staphylococcus aureus*, a common pathogen amongst HAP patients. The aim of the study was to show non–inferiority of ceftobiprole to ceftazidime plus linezolid. It was conducted in April 2005 and May 2006 in 157 sites in Europe, North and South America, and the Asia-Pacific region.

The data visualisation in Figure 3 provides an illustration of the time course of events for the ceftobiprole group (only the ceftobiprole group is displayed here, but a similar picture can be found in the ceftazidime plus linezolid group). On the x-axis, time from randomisation, which equals time from treatment, is shown. Individuals are ordered according to their time on treatment. Clinical cure was recorded in a TOC within a time frame of 7 to 14 days after the end of treatment, displayed in the form of grey-filled dots after the grey lines describing the time on treatment. The follow-up time was more than 30 days for most patients, and it can be seen that many patients die shortly after randomisation (bottom left black-filled dots), probably because of their underlying disease. Censoring is rare before day 28 (few unfilled dots on the left-hand side), and, obviously, death from any cause acts as a competing event (bottom left black-filled dots). Patients dying after cure are marked with a cross.

The primary endpoint was clinical cure at the TOC visit, and the secondary endpoint included all-cause mortality (often 28 days after randomisation). With the protocol-defined non–inferiority margin of −15%, risk differences of proportions of cured patients (ceftobiprole minus ceftazidime plus linezolid) showed that ceftobiprole is non-inferior to ceftazidime plus linezolid for patients with HAP (781 patients) and HAP excluding VAP (571 patients), but non–inferiority was not demonstrated in VAP patients (210 patients).[39] Repeating the analysis with risk differences and confidence intervals for the proportion of patients cured and alive at day 30 in comparison to risk differences and confidence intervals for the proportion of cured patients

showed consistent results due to very few transitions from cure to death: The risk difference for overall cure rates of ceftobiprole versus ceftazidime plus linezolid is −2.95 with a 95% confidence interval of −9.96to4.06[39]; concerning only patients cured and alive at day 30, we got a risk difference of −2.43(−9.44 to 4.58). In HAP excluding VAP patients, a risk difference for cure rates of 0.78(−7.28to8.84) was reported in Awad et al,[39] and for cured and alive at day 30, we calculated 1.51(−6.62to9.63). Finally, in the subset of patients with VAP, a risk difference of −13.72(−25.96to − 1.47)

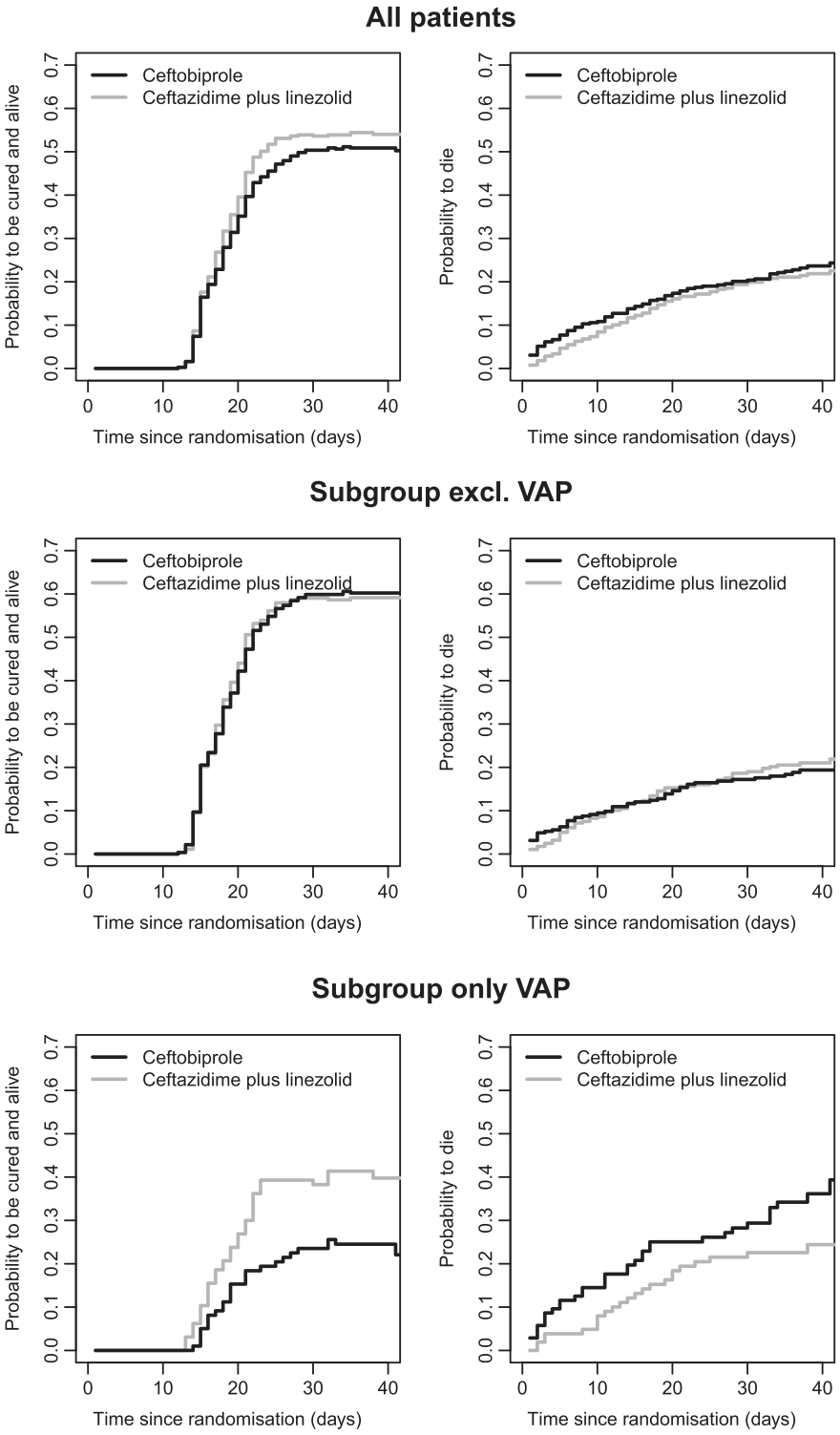


**FIGURE 4** Transition probabilities derived from the Aalen-Johansen estimator using data from a double-blind, randomised, and multicentre trial of patients with HAP/VAP treated with ceftobiprole or ceftazidime plus linezolid.[39] Left: probability to be cured and alive; right: probability to die. HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

was reported,[39] whilst for cured and alive at day 30, we calculated −13.77(−25.64to − 1.90).

One of the problems arising was that for patients who achieved the cure state after the TOC, this was not recorded anymore. A consequential special feature of the given data is that patients after the TOC or patients who experienced a clinical failure are no longer under risk for transition from randomisation to cure in Figure 1. Thus, the test statistics have to be extended to be suitable to the model in Figure 2. Here, an additional state "failure" is used for patients where systemic nonstudy antibiotics between baseline and the TOC visit for the treatment of pneumonia were received or an adverse event occurred. The restricted logrank-based test reveals a non-significant difference between the treatments for all patients ($P = .25$) and the subset of patients with HAP excluding VAP ($P = .91$) and a significant difference for the VAP patients ($P = .01$).

We further studied the influence of the intermediate event time, the time to cure, on the mortality transition of cured patients using a Cox proportional hazards model.[32] We kept the waiting time in state 1 in a regression model for the 12 hazard.[45] This model reported a non–significant coefficient ($P = .73$) for the time to cure, and, therefore, we considered the Markov assumption to analyse this data.

The temporal dynamic of the probability to be cured and alive and the probability to die can be displayed by the cure-death model using the Aalen-Johansen estimator shown in Figure 4. The transition probabilities on the right side show the probability to die, regardless of whether patients were cured before or not, that is, 1 minus the Kaplan-Meier estimator. For the entire sample and the HAP excluding VAP group, the probability curves are comparable across treatment groups. In the VAP-only group, the probability to be cured and alive diverges slowly with progressing time and the probability to die diverges in the first days favouring ceftazidime plus linezolid. For the pseudo-value regression, we investigated the effect over the whole time frame including ten times equally distributed ($s_k = \{12, 15, 18, \ldots, 39\}$) and at day 30 ($s_k = 30$). This technique yields a significant difference only for the subgroup of patients with VAP, $CRR = 0.55$ (0.35-0.87) (whole time frame) and $CRR = 0.58$ (0.38-0.89) (at day 30). For the subgroup of patients with HAP, it results into $CRR = 0.92$ (0.80-1.05) (whole time frame) and $CRR = 0.92$ (0.80-1.06) (at day 30); for HAP excluding VAP, it is $CRR = 1.00$ (0.87-1.15) (whole time frame) and $CRR = 1.00$ (0.88-1.15) (at day 30). An overview of results can be found in the upper part of Table 1.

Additionally, to only examine the overall probability to die, we performed a simple logrank test, yielding a $P$ value of .62 for the whole group, $P = .54$ for the subset of patients with HAP excluding VAP, and $P = .07$ for the VAP patients.

## 4 | SIMULATION STUDY

The purpose of the following simulation is to demonstrate how the cure-death model handles simple and complex treatment imbalances. For ease of illustration, we assume the transition hazards to be constant. Also, no additional censoring was generated. Data was created according to Beyersmann et al.[45] For the standard treatment "treatment B," we chose time constant hazard rates $\lambda^B_{01} = 0.07$, $\lambda^B_{02}(t) = 0.04$,

**TABLE 1** Test statistics and corresponding $P$ values for the chi-squared test for equality of proportions cured ($\chi^2$test cure), the chi-squared test for equality of proportions cured and alive at day 30 ($\chi^2$test cure+alive), the restricted logrank-based test for the difference of 2 transition probabilities (RL-test), and the pseudo-value regression results using 10 times equally distributed over the whole time frame [Pseudo (all)] and at day 30
[Pseudo (30)]

| Real data example | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $\chi^2$ test cure | | $\chi^2$ test cure + alive | | RL test | | Pseudo (all) | Pseudo (30) |
| Subgroup | stat | *P* value | stat | *P* value | stat | *P* value | *CRR* | *CRR* |
| All patients | 0.57 | .45 | 0.37 | .54 | 1.30 | .25 | 0.92 (0.80-1.05) | 0.92 (0.80-1.06) |
| Excl. VAP | 0.01 | .92 | 0.08 | .78 | 0.01 | .91 | 1.00 (0.87-1.15) | 1.00 (0.88-1.15) |
| Only VAP | 4.07 | .04* | 4.36 | .04* | 6.74 | .01* | 0.55 (0.35-0.87)* | 0.58 (0.38-0.89)* |
| **Simulated data (rejection frequencies)** | | | | | | | | |
| **Scenario** | **$\chi^2$ test cure** | | **$\chi^2$ test cure + alive** | | **RL test** | | **Pseudo (all)** | **Pseudo (30)** |
| 1 | 98 | | 35 | | 100 | | 97 | 49 |
| 2 | 3 | | 93 | | 100 | | 87 | 98 |
| 3 | 100 | | 99 | | 87 | | 90 | 93 |
| 4 | 100 | | 100 | | 100 | | 100 | 100 |
| 5 | 34 | | 50 | | 13 | | 8 | 42 |

Abbreviation: RL, restricted logrank; VAP, ventilator-associated pneumonia.
The upper part represents the results for the subgroups of the ceftobiprole trial,[39] where the test statistic (stat) and $P$ value is given for the $\chi^2$ tests and the RL test and the cure risk ratio (*CRR*) is given for the pseudo-value regression. The lower part displays the five different simulation scenarios, where frequencies of rejection of the null hypothesis (treatment equality) for 100 simulated studies are displayed.

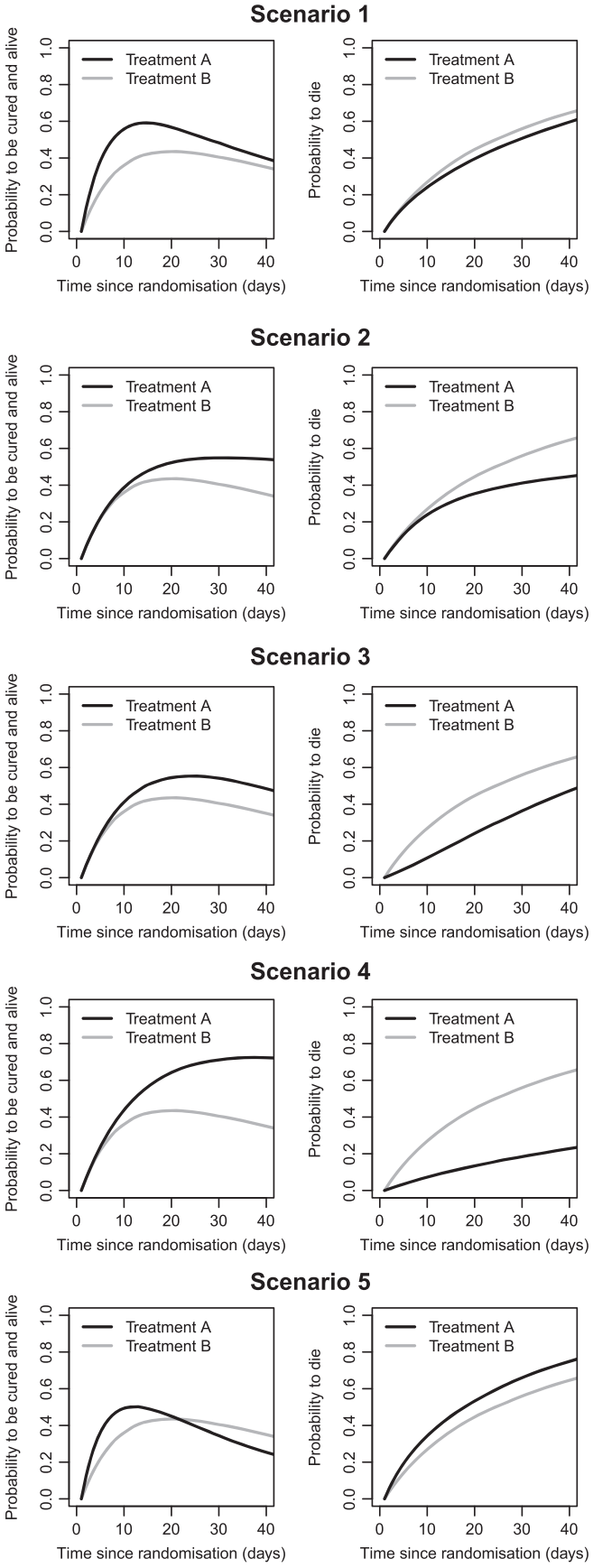


**FIGURE 5** Transition probabilities derived by the Aalen-Johansen estimator for the simulation scenarios with 300 individuals in each treatment group and 100 simulated studies. The curves represent the mean over 100 studies. Left: probability to be cured and alive; right: probability to die

and $\lambda_{12}^{B} = 0.02$. Several simulation scenarios for the new treatment "treatment A" were examined for a treatment comparison with 300 individuals in each treatment group and 100 simulated studies. Superiority regarding cure stands for a higher cure rate whereas superiority regarding death involves a lower death rate. The cause-specific hazard ratio (CSHR) is given for transition 01 and 02 and the hazard ratio for transition 12; treatment differences are marked in bold:

- Scenario 1: Treatment A is superior in the cure rate, $\boldsymbol{\lambda_{01}^{A} = 0.14}$ (CSHR = 2), $\lambda_{02}^{A} = 0.04$ (CSHR = 1), and $\lambda_{12}^{A} = 0.02$ (HR = 1)
- Scenario 2: Treatment A is superior for death after cure, $\lambda_{01}^{A} = 0.07$ (CSHR = 1), $\lambda_{02}^{A} = 0.04$ (CSHR = 1), and $\boldsymbol{\lambda_{12}^{A} = 0.005}$ (HR = 0.25)
- Scenario 3: Treatment A is superior for death without being cured, $\lambda_{01}^{A} = 0.07$ (CSHR = 1), $\boldsymbol{\lambda_{02}^{A} = 0.01}$ (CSHR = 0.25), and $\lambda_{12}^{A} = 0.02$ (HR = 1)
- Scenario 4: Treatment A superior in both mortality rates, $\lambda_{01}^{A} = 0.07$ (CSHR = 1), $\boldsymbol{\lambda_{02}^{A} = 0.01}$ (CSHR = 0.25), and $\boldsymbol{\lambda_{12}^{A} = 0.005}$ (HR = 0.25)
- Scenario 5: Treatment A is superior in the cure rate but worse in mortality rates, $\boldsymbol{\lambda_{01}^{A} = 0.14}$ (CSHR = 2), $\boldsymbol{\lambda_{02}^{A} = 0.06}$ (CSHR = 1.5), and $\boldsymbol{\lambda_{12}^{A} = 0.03}$ (HR = 1.5).

In Figure 5, the probability to be cured and alive for treatments A and B is displayed. In Figure 6, risk differences with 95% confidence intervals can be seen with a hypothetical non-inferiority margin of −15%. For both, mean values over 100 studies are presented.

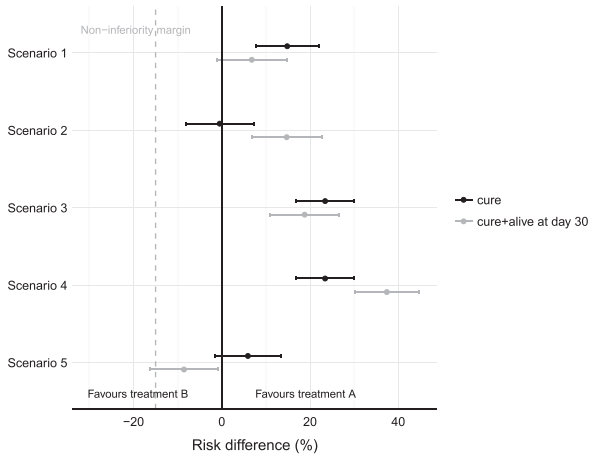


**FIGURE 6** Risk differences with 95% confidence intervals for the simulation scenarios with 300 individuals in each treatment group and 100 simulated studies. Mean values over 100 studies are presented where the non–inferiority margin was set to −15%. The risk differences using overall proportions of cured patients are displayed in black, as typically used in trials for the comparison of two antimicrobial therapies with primary endpoint, eg, clinical cure at the test-of-cure visit. The risk differences using proportions of patients cured and alive at day 30, as proposed analysis strategy, are displayed in grey

In Scenario 1, treatment A is superior concerning cure. The overall risk difference for cured patients is 14.8%, significantly favouring treatment A. Using only patients cured and alive at day 30, the confidence interval is wider and covers 0 (value of no effect). In Scenario 2, more patients stay alive after being cured for treatment A. Whilst there is no difference in the analysis using only patients cured, the proposed analysis using patients cured and alive shows a significant effect favouring treatment A. In Scenario 3, there is no huge difference amongst the analysis strategies but both measures show a positive effect for treatment A because the competing event "death without being cured" has less impact. In Scenario 4, where treatment A is better in both mortality hazards, the analysis strategies differ substantially since patients rather stay cured and alive, comparable with Scenario 2. It is interesting that in Scenario 5, when analysing proportions of patients cured and alive at day 30, the risk difference is negative and non–inferiority is not given anymore, whilst a positive effect is present using only patients cured. This scenario is motivated by trials with extremely high mortality rates or when a microbiological cure is examined (the pathogen is eradicated, but the patient dies because of a toxic treatment).

In the lower part of Table 1, the rejection frequencies for the null hypothesis of treatment equality are displayed. Results are given for the chi-squared test for equality of proportions cured, the chi-squared test for equality of proportions cured and alive at day 30, the restricted logrank-based test for the difference of two transition probabilities, and the pseudo-value regression results using ten times equally distributed over the whole time frame and at day 30. Using the traditional method (comparing proportions of patients cured), a difference in cure probabilities resulting out of different cure-death transitions (eg, Scenario 2) cannot be detected. For this, the chi-squared test for equality of proportions cured and alive at day 30 performs better. These results are very similar to the pseudo-value regression results comparing transition probabilities at day 30. The restricted logrank-based test detects given treatment differences and is not limited to examining one timepoint only. Pseudo-value regression using 10 times equally distributed over the whole time frame provides a possibility to analyse effects at several timepoints simultaneously and represents the difference between the curves displayed in Figure 5 best. In Scenario 5, interpretation of a combined risk is possible only to a limited extent since it depends on which risk is more important and has a higher weight. For a complete picture, transition probabilities in Figure 5 should be taken into account.

## 5 | DISCUSSION

In the present article, we propose an approach for an RCT design regarding the endpoint evaluation for the development

of antibacterial drugs. With cure and death as combined endpoint, a comprehensive picture of the treatment effect can be obtained. We delineate how the cure-death model, based on the well-known illness-death model, is appropriate to examine the whole time-dynamic process of the probability to be cured and alive by addressing the specific challenge of a high underlying baseline mortality. In particular, multistate methodology accounts for the fact that

- patients might die during the time to cure;
- once cured, patients might still die shortly afterwards.

On the basis of this model, we introduced several possibilities for a treatment comparison. Using risk differences with proportions of patients cured and alive, we can make a statement about cure and mortality concurrently. However, we can make inferences about one timepoint only and, consequently, the result strongly depends on this selected time point. These timepoints are quite heterogeneous amongst trials; see the systematic review of Weiss et al.[4] By not considering the time-dynamic process, much valuable information that may be highly relevant from the patient perspective can get lost. Using transition probabilities, time-dependent effects as, eg, in simulation, Scenario 5, can be made transparent.

We presented the straightforward and easily understandable restricted logrank-based test for a treatment effect introduced by Hsieh et al[31] that targets superiority hypotheses. It manages the ordered nature of cure and death and adjusts for a desired prolonged stay in the cure state. However, no single statistic is solely sufficient for the description of this setting. A further limitation of this test is that non–inferiority analyses are not possible due to the quadratic form of the test statistic, it is suitable only for superiority analyses. The benefits of newly developed treatments are often only marginal over existing treatments, and non–inferiority analyses are indispensable. Thus, we recommend to look at the transition plots in combination with a treatment comparison based on pseudo-values, for which non–inferiority analyses are possible using a cure risk ratio. Now, we are also able to better understand the aetiological time-dynamic process on how the new treatment influences the cure process by taking account of death as competing event and the possibility that cured patients might still die shortly after cure. Using the probability of being cured and alive, that is highly meaningful for patients, the time-dynamic process can be revealed, which otherwise tends to be neglected by only regarding proportions of cured patients. The Aalen-Johansen estimator allows us to get a visual overview of (probably hidden) treatment effects that may provide an indication for, eg, a change of dosage. Note that this reduces to the classical Kaplan-Meier estimator for a simple two-state survival setting. The proposed pseudo-value regression does not only allow to test for treatment differences but also to adjust for several covariates. With cure and death as two primary endpoints, a combination of non–inferiority and superiority study can be performed. A test of treatment effect concerning the probability to die can be done via a simple hazard ratio.

Problems arise with the estimation of transition probabilities if the Markov property is violated. Whilst the transition probabilities of continuous-time Markov chains are computed using the Chapman-Kolmogorov equations, which can be solved analytically, the consistency of these estimators cannot be ensured in general for non-Markov processes. Alternative estimators of the transition probabilities not relying on the Markov assumption were firstly proposed by Meira-Machado et al[48] and Amorim et al[49] and further extended by Allignol et al[50] and de Uña-Álvarez et al.[51] A time-varying effect of an intermediate state ought not to be neglected. Meier-Hirmer and Schumacher[52] propose several methods that investigate whether and if how the hazard ratio for the transition after an intermediate event depends on the waiting time to occurrence of this event and/or the sojourn time in this state.

Sample size calculations are challenging if the planned analysis is more complex than, eg, this extended survival setting. The empirical simulation approach of Allignol et al[53] may offer a practical tool to study empirical power and, consequently, to decide on sample size. Based on this idea, an R-based simulation tool is currently developed that enables power calculations and is also applicable to the cure-death model.

In our example, the ceftobiprole trial, we illustrate the advantageous feature of the model in exploiting essential information available in the data that would get lost by only regarding proportions at one prespecified timepoint. We could not only confirm the findings by Awad et al[39] but also provide a new perspective to analyse the data. The simulation study shows that it makes a substantial difference building risk differences out of cured patients or out of patients cured and alive, especially if one treatment is better in the cure rates but worse in mortality rates (Scenario 5) in trials with extremely high mortality rates or when microbiological cure is examined. Generally, this differential effect can appear in both directions.

Another question is not fully addressed: In many trials, as with the ceftobiprole trial, the intermediate cure state is measured only at a single timepoint per patient, eg, when the clinical study investigator performs the TOC. In the ceftobiprole trial, this was mostly performed within a time frame of 7 up to 14 days after the end of treatment. Hence, strictly speaking, we do not know the exact onset time of the intermediate condition cure, the time is therefore interval censored. More advanced statistical methods are required to address this problem and are also part of our ongoing work. Furthermore, there is no unique definition of cure available. An efficacy endpoint is mostly based on resolution and improvement of signs and symptoms of infection at a timepoint after

completion of therapy,[5] but a systematic review of Weiss et al[4] shows that no agreement has been reached neither in the definition of cure nor in the time the TOC is performed.

In conclusion, the cure-death model provides a framework that enables a simultaneous analysis of both endpoints, cure and death. Hereby, a better understanding on how a new treatment influences the time-dynamic cure process is possible. This may be included into future guidelines containing appropriate recommendations to tackle antimicrobial resistance.

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