Marginal structural and structural nested models for causal inference in hospital epidemiology

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Abbreviations

A-IPCW Augmented Inverse probability of censoring weighted.

AFTM Accelerated failure time model.

ALE Asymptotically linear estimator.

BSI Bloodstream infection.

CAB Central vascular catheter-associated bloodstream infections.

CAN Consistent and asymptotically normal.

CI Confidence interval.

CVC Central vascular catheter.

DAG Directed acyclic graph.

ECDC European center of disease prevention and control.

EXPDR Exposure risk doubly-robust.

GEE Generalised estimating equations.

HAI Healthcare-associated infection.

HELICS Hospitals in Europe link for infection control through surveillance.

HR Hazard ratio.

ICA Ignorable censoring assumption.

ICU Intensive care unit.

IPC Inverse probability of censoring.

IPCW Inverse probability of censoring weighted.

IPE Inverse probability of exposure.

IPECW Inverse probability of exposure and censoring weighted.

IPH Scientific institute of public health.

IPW Inverse probability weighted.

IQR Interquartile range.

LOS Length of stay.

MSPHM Marginal structural proportional hazards model.

MSPHM-P Marginal structural proportional hazards model for partial exposure regimes.

NSIH National surveillance of infections in hospitals.

NSIH-ICU National surveillance of infections acquired in intensive care units.

RAL Regular and asymptotically linear.

RMM Restricted moment model.

SAPSII Simplified acute physiology score II.

SFTM Structural accelerated failure time model.

SNFTM Structural nested accelerated failure time model.

SRA Sequential randomisation assumption.

TTP Trusted third party.

VAP Ventilator-associated pneumonia.

CHAPTER 1

Introduction

1.1 Attributable mortality of healthcare-associated infections

A Healthcare-associated infection (HAI) is defined as an infection which was not incubating at the time of admission to the hospital, usually occurring 48 hours or more after admission (American thoracic society and Infectious diseases society of america, 2005; Valles and Ferrer, 2009). HAI is common in hospitals worldwide. The European point-prevalence survey of HAI and antimicrobial use 2011-2012 (ECDC, 2013) found a prevalence for Belgium of 7.1% infected patients, with intensive care the unit type that is most affected (20.3% prevalence). HAI has long been recognised as an *adverse event* in clinical care, meaning that it has the potential of worsening a patient's health status once it occurs and of being preventable (Valles and Ferrer, 2009; Chastre, 2005). It is understood that by preventing infection in a patient in acute care, the risk that this patient dies or needs extra care, can be reduced. Both these statements, the feasibility of measures for the prevention of

infection and the effects of infection on mortality and morbidity, are supported by a vast literature in hospital epidemiology and clinical care.

In what follows we elaborate in particular on the attributable effect estimation of HAI. Knowing the exact effects of infection is considered important, since it guides clinicians in prioritising the care of patients with infection, it guides patients and their relatives on the excess risks of mortality and morbidity, and it guides hospital staff and external partners on the expected outcomes when investing in or adopting novel strategies for the prevention of infection (Muscedere, 2009).

Despite the assumed adverse effects of infection on a patient's health, studies on attributable mortality effect estimation of infection give controversial results, with results that describe this effect as being neutral to extremely risk increasing (Carlet, 2001; Muscedere et al., 2010; Timsit et al., 2011; Klompas, 2009; Nguile-Makao et al., 2010; Melsen et al., 2009; Siempos et al., 2009; Renaud and Brun-Buisson, 2001; Rello et al., 2000; Digiovine et al., 1999; Rello, 1999). Various explanations can be given for this. First, no unified case definitions exist for HAI, meaning that it is difficult to pinpoint the literature on this subject if it uses different methods to asses HAI. Second, data on this subject is derived from different study types, ranging from prospective surveillance studies towards retrospective case-cohort design or data derived from administrative databases. Third, different populations are often studied, from single-center intensive care units within tertiary hospitals with a specific patient population to national or even multinational multicentric studies having a substantial heterogeneity of units and medical practice, and therefore of the incidence of HAI, mortality and prognostic factors. Fourth, only a minority of studies provide details on the appropriateness of the treatment for infection, while it is agreed that presence or absence of this is pivotal for patient outcome. Fifth, it is well acknowledged that the effect of HAI on mortality or morbidity needs to be carefully adjusted in order to separate the effect of HAI from those of underlying prognostic factors prior to infection, both intrinsic (related to the patient's profile) and extrinsic (related to the treatments the patients receives) factors. Indeed, groups of patients with and without infection will to a certain extent be unbalanced in terms of prognostic factors for mortality and infection, which leads to *confounding* of the infection-mortality association. Because of

this, adjustment for such prognostic factors in any estimation procedure will be necessary. Additional adjustment may be needed when only patient follow-up data within the hospital or ward is available for analysis, as is usually the case. When studying mortality, this means that a group of subjects has an unobserved outcome event and correspondingly a *censored survival time*. This censoring occurs when a patient dropped out from follow-up, or in this case is being discharged alive from the hospital or ward. When the reasons for censoring are linked to the outcome event itself, as will be the case here because a patient will mostly be discharged from the hospital for health reasons, then further adjustment is needed for this so-called *selective drop-out*. In the literature, these adjustments are not always performed, and even so, a wide variety of models and adjustment methods are used, not all of which are appropriate.

This thesis looks more deeply at the statistical estimation of the attributable mortality of infection. We will start with explaining how we collected the data that we used for our analysis. These are derived from the *National surveillance of infections acquired in intensive care units (NSIH-ICU)* (Section 1.2, Chapter 2), a longstanding national surveillance study for monitoring the incidence of HAI, which has lead to a rich database of participating hospitals, patients, collected outcomes, and risk factors. Over the years, the NSIH-ICU data have become an appropriate basis for estimation of attributable effects of infection. This is due to the many risk factors that are collected during surveillance, which form a description of a patient's health status or therapeutic activity, and therefore can be considered as prognostic variables for mortality. Such variables are ideal candidates when wanting to adjust the estimated crude effect of HAI on mortality for underlying patient health, and as such come to an estimated effect that is as much as possible attributable to the onset of HAI (Samore et al., 2007; Soufir et al., 1999; Heyland et al., 1999; Fagon et al., 1996).

In Sections 1.3 and 1.4 of this Introduction, we explain why we have chosen two types of estimators as the basis for estimating the attributable effect of HAI on mortality. These are *Inverse probability of exposure and censoring weighted (IPECW) estimation under a Marginal structural proportional hazards model (MSPHM)*, and *Inverse probability of censoring weighted (IPCW) G-estimation under a Structural*

nested accelerated failure time model (SNFTM). These are estimators of *causal effects*, meaning that they deliver unbiased effects in larger samples, or that the estimated effect does not deviate systematically from the true effect. We will demonstrate that this is a challenge given the observational nature of the study, the time-dependent exposure to HAI, the presence of time-varying prognostic factors that can act as cause and effect of HAI and as such lead to time-varying confounding of the infection-mortality relation, and the selective drop-out of patients under surveillance. Given the specific features of our data, the studied exposure and outcome, we will then describe relative risks for describing attributable effects with causal interpretation, and the underlying assumptions of our analysis that allow us to identify these. We will then demonstrate why, in this context, standard regression models usually fail in delivering such effects, as opposed to aforementioned estimators.

The IPECW estimator under a MSPHM is then applied and further developed in Chapters 3 and 4 respectively, while the IPCW G-estimator under a SNFTM is further developed and applied in Chapter 5. Finally, Chapter 6 closes this thesis by summarising the found results, and presenting further comments and ideas for the future.

1.2 National surveillance of infections acquired in intensive care units

The *National surveillance of infections acquired in intensive care units (NSIH-ICU)*, organised by the *Scientific institute of public health (IPH)*, is an observational study on the incidence of Healthcare-associated infection (HAI) in the Intensive care unit (ICU). Its objectives are to standardise data collection on infection incidence within the ICU across acute care hospitals in Belgium, and to collect national reference data on the incidence of ICU-acquired infection. Both these aspects, standardisation of methods and collection of reference data, then allow the monitoring of trends on a hospital and a multicentric (regional, national, European) level and the comparison of infection rates between hospitals. The NSIH-ICU study

uses the concept of clinical surveillance, applies it to ICU-acquired infections and extends it towards a national level. Surveillance is here defined as the collection of data on particular clinical events and analysing and interpreting its results in light of historic data (trend analysis) or data of other hospitals (benchmarking with reference data). When done continuously and systematically, surveillance has proven to be an essential part in a strategy for the prevention of infection, specifically when it targets HAI as an adverse clinical event, when it measures its incidence, and when its results are interpreted with the concerned hospital staff (Haley et al., 1985; Gastmeier et al., 2000b).

Surveillance of HAI within intensive care is one of the principal types of surveillance for HAI. This is due to the high prevalence of infections among intensive care patients, which results in measures of infection incidence that are both precise and reducible. The focus on the intensive care environment makes this surveillance also relatively more feasible from a practical point of view as compared to other types of surveillance that cover the entire hospital. Such practical considerations are important, for example when unit staff needs to be trained for epidemiological case definitions, or when data collection needs to be organised. A high involvement of unit staff also guarantees a prospective data collection, which is considered advantageous in terms of completeness and quality of data as compared to retrospective studies. Such prospective data collection will be beneficial in implementing a culture of increased awareness for the studied event, and can therefore be instrumental in the prevention of such events and in limiting its attributable mortality and morbidity (Blot, 2008).

Because the NSIH-ICU surveillance is multicentric, it provides to a certain extent representativeness with the Belgian ICU population for the studied time period. This refers particularly to the inclusion of ICU units from primary and secondary hospitals, which are often lacking in literature reports on attributable mortality of infection that are mostly done by groups from tertiary (teaching and academic) centres. The amount of data collected also allows deeper investigation of attributable effects within particular subgroups of patients, based for example on categories of severity scores. Furthermore, due to efforts during the last two decades at a European level in standardising the methodology of national surveillance of infections

in the ICU, the results of the Belgian surveillance can be compared with those of other networks in Europe and contribute to reference data on infection incidence across Europe (Offical journal of the European communities, 1998, 2009).

Because HAI surveillance occurs within a context of quality improvement of clinical care, the outcomes of such surveillance need to support clinical decisions. Therefore, data collection on infections, their risk factors and outcomes need to have a sufficient level of clinical detail. This is made explicit by the *surveillance protocol*, which is the principal tool for standardisation of data collection over all participating hospitals, and is elaborated in close collaboration with clinicians from hospitals performing infection surveillance. Next to stating the objective of the surveillance, this protocol gives all specifications of the data that is to be collected, including definitions of the types of HAI under surveillance, their risk factors and outcomes.

Case definitions of infections are based on exhaustive lists of clinical signs, symptoms and radiological and microbiological evidence. The collection of data on the occurrence of HAI is called *case-based*, meaning that each individual episode of HAI that occurs within the followed population needs to be documented. This includes the day of infection onset, which allows preciser adjustment of infection incidence, for example on aggregated patient- or device days only occurring before the onset of an infection episode. Data collection on specific characteristics of infections aims to distinguish particular infection subtypes that are the focus of prevention strategies (such as invasive device-associated infections), and also to distinguish the diagnostic strategies within hospitals for particular infections (for example when due to pneumonia) (Suetens et al., 2002).

The collection of risk factors for infection supports the objective of standardisation of infection rates for factors related to each hospital's or unit's specific patient population. It therefore objectifies a hospital's evolution of its HAI incidence over time, as well as the comparison of its infection incidence with other hospitals (Sax and Pittet, 2002). These risk factors form a description of the patient's health status at admission to the ICU (*intrinsic factors*), or of the therapeutic activity done during a patient's stay at unit (*extrinsic factors*). Risk factor data collection is done on all patients included in the surveillance, therefore making surveillance

also *patient-based*. Furthermore, because the daily infection risk increases with the number of days that a patient remains in the unit, risk factors for infection are also collected on a daily basis.

Other outcomes (next to infections) that are collected are the vital status at discharge from the unit, including the date of discharge which allows calculating the number of patient days for each patient. Knowing these outcomes is important, because they can be used to measure the impact of infection incidence on either mortality, length of stay, or device utilisation. This is done either for a specific period, or by relating the trend in infection incidence to the trend of other measured outcomes.

The surveillance protocol is further complemented by registration software allowing entry and validation of surveillance data locally by the hospital (Freeman et al., 2013), and by feedback reports that calculate relevant indicators on infection incidence, their risk factors and outcomes (Gaynes et al., 2001). The registration software allows in the first place to do manual entry of locally collected surveillance data. A separate module supports the import of existing electronic data. In practice, this is a cumbersome task as many computerised systems in hospitals were initially implemented for administrative purposes. Even when implemented for clinical reasons, these do not automatically serve the objective of epidemiological follow-up, and necessitate expert data querying skills by the hospital (Colpaert et al., 2010). Also, surveillance data in electronic format will need to be collected from many sources, such as databases on admissions, laboratory results or clinical therapies, which renders an integrated automatic re-use even more difficult.

Reporting of surveillance data collected in a multicentric context is a complex task because it needs to be done for each participating hospital or their individual units, and for a particular surveillance year or quarter. In a first stage, reporting is done by the hospital on the local hospital database using the registration software, which allows for a hospital or unit to validate its data before it is decided to send these to the national coordinating center. In a second stage, reporting is done on the national reference data, which enables comparison for each indicator with the relevant percentiles of the national distribution of these indicators, and enables the hospital to position their obtained results within the national distribution.

Results on infection incidence of individual hospitals are considered to be too sensitive to be made publicly available. This is because infections are considered as adverse events; a high incidence can be interpreted as *bad performance* on the hospital's or unit part. However, a hospital is not in complete control of the HAIs that it observes during surveillance, its infection rates are determined by many other factors that are beyond the control of the hospital and its staff. Still, due to this sensitivity, a hospital's specific results together with their comparison with national reference data are only reported to the hospital that contributed the surveillance data. The IPH formally acts here as a *Trusted third party (TTP)*, taking up the role of intermediate between the hospital and the federal government, by feeding back the hospital-specific results only to the hospital itself (as described above), and by reporting results to the Federal or other levels only in aggregated form, not allowing identification of results of individual hospitals. This definition and role of a TTP ensures that valid multicentric data on adverse events can be collected, guaranteeing hospitals confidentiality and preventing their results from being used against them. In other words, it guarantees a non-punitive or -blaming environment (Offical journal of the European communities, 2009; Martin et al., 2013).

1.3 Causal Inference

1.3.1 Notation

Our study follows a cohort of n subjects in time, with measurements at discrete time points $t = 1, ..., T_m$ (with T_m the total follow-up time) of a time-dependent exposure and risk factors, an outcome event, and a drop-out event. In what follows, we will suppress the identifier for subject i if possible. At each time-point, the following random variables are defined: the exposure A, the outcome Y, a vector L of measured prognostic factors affecting both A and Y. Variable U is a vector of unmeasured prognostic factors. The distinction between U and L is essential, as we assume that it is impossible in a collection of observational data to measure every common predictor of exposure and outcome. Variable

C indicates whether the subject is lost to follow-up at a particular time-point, which will lead to Y being unobserved at that time. Variables A, Y and C are dichotomous, taking values 0 (not present) or 1 (present). Variables U and L can be dichotomous, categorical or continuous (or multiples of these combined in a vector). At a particular t, temporal ordering is (U, L, A, C, Y). The full data is the vector of variables $V = (U, L, A, C, Y)$, while the observed data - which is available for analysis - will be the vector $X = \{L, A, C, (1 - C)Y\}$. For any variable Z, a lower case symbol z will indicate one of its possible realisations; the isolated use of such a lower case in a counterfactual outcome (see further) or conditioning statement will indicate "$Z = z$", ie. $Y_z \equiv Y_{Z=z}$ and $E(Y|z) \equiv E(Y|Z = z)$.

All variables defined above are essentially time-varying, meaning that a variable Z can take a value at a particular time point t that is different from its value at the previous time point $t - 1$, Z_t will therefore indicate Z measured at t. Variables A, C and Y are defined to have absorbing states at value 1, meaning that once this value is obtained it will remain so until the rest of the follow-up time. Denote the history of a variable up to time-point t as $\overline{Z}_t = (Z_1, .., Z_t)$, with $\overline{0} = (0_1, .., 0_t)$. Also, let Z_0=0. Let the survival time T be the discrete time from study start at $t = 0$ until the time t at which the event of interest Y occurs.

Applying the above notation to our study of the effect of infection on mortality within the ICU, exposure to infection will be denoted by A, death in the ICU by Y, being discharged alive from the ICU (or lost to follow-up) by C, and the measured prognostic factors by L.

1.3.2 A discrete-time proportional hazards model

We can estimate the effect of exposure A on outcome Y by calculating $\lambda_Y(t|\overline{a}_t)$, which is the conditional hazard of the outcome event for each group of subjects with observed exposure history $\overline{A}_t = \overline{a}_t$. When relying on (semi-)parametric models, this is usually done using a time-dependent Cox proportional hazards model (Hosmer et al., 2008). Also, because our study design is based on discrete time-points at which information on exposure and outcome is collected, we will use the discrete-time representation of the conditional hazard: $P(Y_t = 1|Y_{t-1} = 0, \overline{a}_t)$,

which is the risk of the outcome event Y at time t conditional on Y not having occurred until $t-1$, and on exposure history $\overline{A}_t = \overline{a}_t$ at t. Using the way the data is structured, with one observation for each time a subject is under follow-up, it is straightforward to calculate the discrete-time hazard under the logistic regression model

$$P(Y_t = 1 | Y_{t-1} = 0, \overline{a}_t; \beta^{\text{st}}) = \text{expit}(\beta_0^{\text{st}} + \beta_1^{\text{st}} \overline{a}_t) \tag{1.1}$$

with β^{st} an unknown parameter vector ("st" abbreviation for standard) and $\text{expit}(u) = \exp(u)/\{1+\exp(u)\}$. For the sake of exercise, we used the simplest model possible, thereby ignoring possible time-specific main effects. If we take $\overline{a}_t = a_t$ (therefore assuming one-dimensional β_1^{st}), and assume a rare outcome, or $\text{expit}(u) \equiv \exp(u)$, model (1.1) can now be used to define the following contrast

$$\exp \beta_1^{\text{st}} = \frac{P\{Y_t = 1 | \overline{Y}_{t-1} = 0, a_t = 1; \beta^{\text{st}}\}}{P\{Y_t = 1 | \overline{Y}_{t-1} = 0, a_t = 0; \beta^{\text{st}}\}} \tag{1.2}$$

or the ratio of discrete-time hazards at t for subject-times under observed exposure $a_t = 1$ versus observed exposure $a_t = 0$. Hazard ratio (HR) (1.2) is a *subgroup contrast*; it contrasts a measure of the outcome across subgroups according to exposure status at t and to being alive at $t-1$. Causal interpretation of this contrast is problematic, due to it being defined within subgroups of subjects that are not exchangeable in terms of prognostic factors U and L. In further sections, we will elaborate on how we can arrive at contrasts that do have causal interpretation.

1.3.3 Exposure regimes, potential outcomes and causal contrasts

Let $\overline{a} \equiv \overline{a}_{T_m} = (a_0, a_1, ..., a_{T_m})$, be the *exposure regime set through study end* T_m, and $Y_{t,\overline{a}}$, the *potential or counterfactual outcome of a subject under exposure regime* $\overline{a}$ (Rubin, 1978; Robins, 1986; Hernàn, 2004). $Y_{t,\overline{a}}$ is called a potential outcome, because for each subject it is only potentially observed, or observed counter-to-fact. Using a simplified study design with study end at $T_m = 2$, no drop-out before study end, and taking into account the absorbing state of $A_t = 1$ at any t, each subject

will have three potential outcomes at $T_m = 2$, $\{Y_{t,(0,0)}, Y_{t,(1,1)}, Y_{t,(0,1)}\}$. Of these, only the potential outcome that corresponds to the observed exposure regime will be observed.

Potential outcomes are used to define a *causal* or *population contrast*, which is clearly distinguished from the earlier defined subgroup contrast. Assume that we are able to observe for each subject the potential outcomes under all possible exposure regimes. For now, let us ignore how we achieved this, in further sections we will explain the assumptions and techniques behind the *identification of the mean of potential outcomes*. In the original dataset, each single observation provides for one subject the result of his or her outcome Y_t for exposure $A_t = a_t$ at t. When all potential outcomes are observed, each observation will be augmented according to the number of possible exposure regimes; in our example, each observation will be augmented with two supplementary outcomes, accounting for the two counterfactual outcomes that are unobserved. Using this augmented dataset to fit a logistic regression for the risk of the outcome as a function of exposure regime $\overline{a}$, this will yield:

$$\begin{aligned} P(Y_{t,\overline{a}} = 1 | Y_{t-1,\overline{a}} = 0; \beta^{\mathrm{c}}) &= \text{expit}(\beta_0^{\mathrm{c}} + \beta_1^{\mathrm{c}} a_t) \\ &\quad \text{for all } \overline{a}, t \leq 2 \end{aligned} \tag{1.3}$$

and corresponding contrast

$$\exp \beta_1^{\mathrm{c}} = \frac{P\{Y_{t,(a_1,1)} = 1 | \overline{Y}_{t-1,(a_1,1)} = 0; \beta^{\mathrm{c}}\}}{P\{Y_{t,(0,0)} = 1 | \overline{Y}_{t-1,(0,0)} = 0; \beta^{\mathrm{c}}\}} \text{ for } t \leq 2 \tag{1.4}$$

with β^{c} an unknown parameter vector ("c" abbreviation for causal), of which $\exp \beta_1^{\mathrm{c}}$ is the counterfactual hazard ratio when exposure regime is set to $(a_1, 1)$ versus when exposure regime is set to $(0, 0)$ at $t \leq 2$. Contrast (1.4) uses averages of counterfactual outcomes, and does not suffer from being defined within different (unexchangeable) subgroups of observed exposure history, as was the case with contrast (1.2). We would therefore be tempted to interpret this as a *causal contrast*. This is however problematic, due to the numerator and denominator of (1.4) still conditioning on different subgroups, being $\overline{Y}_{t-1,(a_1,1)}$ and $\overline{Y}_{t-1,(0,0)}$ respectively,

that are not exchangeable in terms of prognostic factors. To resolve this, we can use the predicted hazards of model (1.3) for the calculation of $P(Y_{t,\overline{a}} = 0)$, or the *counterfactual risk of survival under exposure regime* $\overline{a}$ at t, as follows

$$P(Y_{t,\overline{a}} = 0; \beta^{c}) = \prod_{s=1}^{t} \{1 - P(Y_{s,\overline{a}} = 1 | Y_{s-1,\overline{a}} = 0; \beta^{c})\} \tag{1.5}$$

and then construct

$$\frac{P\{Y_{t,(a_1,1)} = 0; \beta^{c}\}}{P\{Y_{t,(0,0)} = 0; \beta^{c}\}} \text{ for } t \leq 2 \tag{1.6}$$

or the *counterfactual survival risk ratio* when exposure regime is set to $(a_1, 1)$ versus when exposure regime is set to $(0, 0)$ at $t \leq 2$. Contrast (1.6) does not suffer from the problems due to conditioning on a counterfactual under different exposure regimes, which makes it a *population* or *causal contrast*, or a contrast that is unconfounded by prognostic factors. We define it as the *total causal effect* of exposure at any time on outcome.

Let us study other causal contrasts of interest, and consider following model:

$$\begin{aligned} P(Y_{t,\overline{a}} = 1 | Y_{t-1,\overline{a}} = 0, \beta^{c,1}) \quad &= \quad \text{expit}\{\beta_0^{c,1} + \beta_1^{c,1} a_1 \\ &\quad + \beta_2^{c,1} a_2 (1 - a_1)\} \\ &\quad \text{for all } \overline{a}, t \leq 2 \end{aligned} \tag{1.7}$$

with $\beta^{c,1}$ an unknown parameter vector, of which $\exp \beta_1^{c,1}$ is the hazard ratio when exposure regime is set to $(1, 1)$ versus when exposure regime is set to $(0, 0)$, and $\exp \beta_2^{c,1}$ is the hazard ratio for subjects under exposure regime $(0, 1)$ versus exposure regime $(0, 0)$. Using formula (1.5) to convert hazards in survival risk, we can decompose causal contrast (1.6) into contrasts that will give us insight into the time-varying nature of the causal effect of exposure on outcome, and as such be able to estimate lag-effects of exposure. This is because $\beta_1^{c,1}$ and $\beta_2^{c,1}$ parametrise the effect of exposure starting at time-points $t = 1$ and $t = 2$ respectively. After conversion to counterfactual survival risk and when compared to exposure regime $\overline{a} = (0, 0)$, these parameters will measure the *total* or *overall effect* of exposure at

$t = 1$ and $t = 2$ on outcome.

Furthermore, contrast $\exp(\beta_1^{c,1} - \beta_2^{c,1})$ is the hazard ratio when exposure regime is set to $(1, 1)$ versus when exposure regime is set to $(0, 1)$. The corresponding counterfactual survival risk ratio measures the *controlled direct effect* (Robins and Greenland, 1992; Vansteelandt, 2012) of exposure at $t = 1$ on outcome at $t = 2$, so-called because the only difference between these two exposure regimes is the setting of exposure at $t = 1$ to 0 or 1, with exposure at $t = 2$ being fixed to "exposed". From the above arguments, we call (1.7) a model for the *joint causal effect of exposure*.

1.3.4 Identifying conditions

As explained above, potential outcomes are an abstract concept, ie. for each subject only one potential outcome for each subject-day will be observed by definition, with the distribution of potential outcomes under remaining exposure regimes needing to be identified. The identification of the average of a potential outcome [such as the numerator or denominator of contrast (1.4)] is possible under a set of *identifying assumptions for causal inference* (Rosenbaum and Rubin, 1983), stated as follows and explained one by one hereafter:

$$\begin{aligned} \text{Consistency of exposure regime} \quad &: \quad Y_{t,\overline{a}} = Y \text{ if } \overline{A} = \overline{a} \\ &\quad\;\; \text{for all } \overline{a}, t \qquad (1.8) \\ \text{Sequential randomisation of exposure} \quad &: \quad Y_{t,\overline{a}} \amalg A_s | y_{s-1} = 0, \overline{a}_{s-1}, \overline{l}_s \\ &\quad\;\; \text{for all } t, s \leq t, \overline{a}_{s-1}, \overline{l}_s \qquad (1.9) \\ \text{Positivity of exposure risk} \quad &: \quad P(A_t = a_t | y_{t-1} = 0, \overline{a}_{t-1}, \overline{l}_t) > 0 \\ &\quad\;\; \text{for all } \overline{a}_t, t \qquad (1.10) \end{aligned}$$

Consistency assumption (1.8) states that a subject's potential outcome under her actually observed exposure regime is precisely her observed outcome. Under this assumption, the mechanisms under which the exposure regime $\overline{a}$ was set, may

have no other hypothesised influence on the outcome Y than by setting the actual exposure. It therefore calls for the definition of realistic exposure regimes, and their corresponding potential outcomes, when relying on these for effect estimation. More specifically, one needs to be able to explain how a particular exposure regime could hypothetically be assigned to a subject that was in reality exposed to a different regime. Also, such exposure regime should be in correspondence with the study that generated the data (Hernàn and Taubman, 2008). Applied to our study, potential outcome *risk for mortality under presence (or absence) of exposure to infection* needs to be unambiguously defined. By defining *the effect that would be seen in patients if infection would be prevented* (Fagon et al., 1993, 1996; Bonten et al., 2004; Rello and Valles, 1998), some authors already have phrased the research question in causal terms, however without resorting to estimators that directly involve potential outcomes. In Section 1.2, we explained that the surveillance study that gave rise to our data is actually part of a strategy for the prevention of infections; hypothesising about the counterfactual outcome *mortality when infections are prevented* is therefore a valid exercise, as such an outcome is both realistic as well as imaginable in the data we use for this study.

The consistency assumption for causal inference has received attention in response to a few studies that look at exposures that could not be immediately considered as realistic interventions, nor were the potential outcomes under this exposure immediately realistic for the studied population (Cole and Frangakis, 2009; Vanderweele, 2009; Haight et al., 2005). For example, in a study of the causal effect of body mass index (BMI) or body composition on mortality (Hernàn and Taubman, 2008), it is unclear how a studied population could be assigned a particular BMI, because experiencing a certain BMI at a certain moment is assumed to depend on a complex series of biological pathways. Also, even when these pathways are known in such a way that the investigator knows how to arrive at a particular BMI at a particular time, it is not unrealistic that some pathways that lead to exposure would also be related to outcome in other ways than by influencing exposure. As a result, two pathways that lead to the same exposure level might still lead to different outcomes, resulting in ill-defined potential outcomes. Applied to our study, imagine for example an exposure regime “absence

of infection" hypothetically generated by a profylactic drug that not only kills off a pathogen but also independently worsens a patient's prognosis as a side effect. The potential outcome generated under such regime would be ill-defined because the pathways that generate such a regime influence the outcome by other ways independently of the regime itself.

The *Sequential randomisation assumption (SRA)* (1.9) states that, conditional on survival, exposure and confounder history $(\overline{Y}_{t-1}, \overline{A}_{t-1}, \overline{L}_t)$, the potential outcome $Y_{\overline{a}}$ is independent of exposure A at t. It says that exposure at t is randomised within levels of exposure and measured confounder history at t, in other words that exposure is *sequentially randomised*. This means that, although the overall groups formed by exposure may be non-comparable in terms of L, they will become comparable sequentially within the levels formed by $(\overline{Y}_{t-1}, \overline{A}_{t-1}, \overline{L}_t)$. We assume that sequential randomisation holds within levels of measured prognostic factors $\overline{A}_{t-1}$ and $\overline{L}_t$, which is more strict than when this would also include the unmeasured $\overline{U}_t$, and therefore this assumption is also known as the assumption of *No unmeasured confounders* (Rosenbaum and Rubin, 1983). Informally, it says that history of exposure and measured confounders is sufficient in adjusting the exposure-outcome association at t.

The assumption of *Positivity of the risk of exposure* (1.10) states that within each stratum defined by the measured confounder history $\overline{L}_t$, there is variation in the exposure. In other words, there may be no levels of confounders where no subjects in the population are (un)exposed, or generally where exposure is deterministically set. Because of this, this assumption is also referred to as the assumption of *Experimental treatment assignment* (van der Laan and Robins, 2003).

As an example, we consider a study with a single time point $T_m = 1$, and verify how we can use aforementioned assumptions to identify the average of a potential outcome $E(Y_a)$. With a single time-point, these assumptions will be: *Consistency of exposure*: $Y_a = Y$ if $A = a$ for all a; *Conditional randomisation of exposure*: $Y_a \amalg A|l$ for all l; *Positivity of exposure risk*: $P(A = a|l) > 0$ for all a.

$$\begin{aligned} E(Y_a) &= E\left\{E(Y_a|L)\right\} \\ &= E\left\{E(Y_a|a, L)\right\} \end{aligned}$$

$$= \quad E\left\{E(Y|a, L)\right\} \tag{1.11}$$

the first equality is due to conditional expectation (Casella and Berger, 2001), the second to conditional randomisation, the third to consistency of exposure, and positivity of exposure risk is needed to identify $E(Y|A = a, L)$. Equation (1.11) shows how to identify the potential outcome from the observed data by means of *standardisation*: calculating the outcome's mean for particular values of the exposure regime conditional on prognostic variables, and averaging this towards the risk of the marginal realisations of the prognostic variables, this last step being called standardisation. Further on, we will use standardisation in the setting of time-varying exposure regimes.

1.3.5 Censoring of survival time

As introduced above, observation of the outcome Y_t depends on whether the subject did not drop-out at or before t, which is encoded in C_t (with values 1 in case of drop-out and Y_t missing, 0 if not). The same applies to observation of exposure and prognostic variables A_t and L_t, which will be only observed when $C_{t-1} = 0$. Due to this, we need to append $c_{t-1} = 0$ to the conditioning events of SRA (1.12) and Positivity (1.10).

Variable C is called the *Censoring event* because it encodes information on censoring of the survival time. Because censoring might lead to a selective subset of subjects relative to the studied source population (see further), our aim is to identify the distribution of the outcome for those subjects that drop-out, in analogy to the identification of potential outcomes defined in terms of exposure regimes. In order to identify Y under missingness, we adapt assumptions (1.8-1.10) for identifying potential outcomes as follows (Rubin, 1976; Robins et al., 1994):

Ignorable censoring assumption (ICA): we assume that, at any time-point, censoring is independent of the counterfactual outcome, conditional on neither the outcome nor censoring having occurred, and on the history of exposure and of risk

factors for censoring and outcome up to that time:

$$Y_{t,\overline{a}} \amalg C_t | y_{t-1} = c_{t-1} = 0, \overline{l}_t, \overline{a}_t \text{ for all } \overline{a}_t, \overline{l}_t, t \tag{1.12}$$

It follows that past exposure and confounder history until t suffices to predict censoring at t, without needing any other information at or after t. This means that conditional on confounder history up to time t, censoring holds no information about future survival.

Positivity of risk of remaining uncensored: we assume that the risk of staying uncensored exceeds 0 within levels of exposure and confounder history, or

$$\begin{aligned} &P(C_t = 0 | y_{t-1} = c_{t-1} = 0, \overline{a}_t, \overline{l}_t) > 0 \\ &\text{with probability } 1 \end{aligned} \tag{1.13}$$

We repeat earlier procedure of standardisation (1.11) to identify Y_a in a study with $T_m = 1$. The above assumptions will then be: *Ignorability of censoring*: $Y_a \amalg C | l, a$ for all l, a; *Positivity of risk of remaining uncensored*: $P(C = 0 | a, l) > 0$ with probability 1.

$$\begin{aligned} E(Y_a) &= E\{E(Y_a|L)\} \\ &= E\{E(Y_a|a, L)\} \\ &= E\{E(Y_a|a, L, c = 0)\} \\ &= E\{E(Y|a, L, c = 0)\} \end{aligned} \tag{1.14}$$

with the first equality due to conditional expectation, the second due to SRA, the third to ICA, and the fourth to consistency of exposure regime. The average in the last line of (1.14) assumes positivity of the risks of exposure and censoring.

1.3.6 Causal directed acyclic graphs

We will now explain why, in the presence of time-varying and intermediate confounders, standard techniques for the adjustment of confounders may fail to esti-

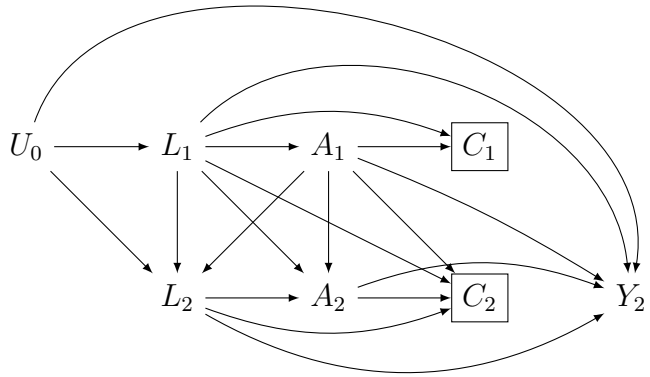


Figure 1.1: Causal directed acyclic graph for the effect of A_1 and A_2 on Y_2.

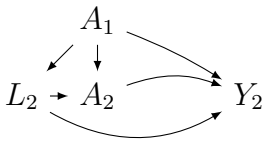
mate unbiasedly the causal contrasts as defined above. To do so, causal diagrams are a powerful tool to visualise variables, their relationships and the assumptions that encode these, and to reveal possible biases occurring in the estimation of causal effects (Pearl, 1995; Hernàn et al., 2004, 2002; Vanderweele and Robins, 2007). Figure 1.1 is a causal diagram that shows the random variables defined in Section 1.3.1 by means of nodes, in the temporal order of occurrence (top left occurs earliest, bottom right last) and their possible causal relations by means of directed edges. The diagram depicts variables and their relationships for 2 time-points $t = 1$ and $t = 2$, except for U which will be only defined as baseline variable at $t = 0$, however the results that follow remain valid under a time-dependent U.

Essential to our diagram is that any defined relation between variables depicted in the diagram is directed, meaning that each edge has only one arrow, and that the diagram is acyclic, meaning that one can never start from one variable and end up at the same variable by following the direction of the arrows. The diagram in Figure 1.1 follows these constraints, and is therefore also called a *Directed acyclic graph (DAG)*. Two supplementary constraints are needed in order for such DAG to be called *causal*, 1) the absence of a directed edge between two variables in the DAG represents the assumption of absence of a direct causal effect between these variables (which does not mean lack of association, see further), and 2) the DAG

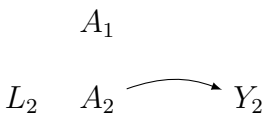
must incorporate all common causes of any 2 variables in the diagram.

The relationships in Figure 1.1 are explained as follows. Following the last requirement of the previous paragraph, variables U_0, L_1 and L_2 need to be part of the diagram because they are common causes of A_1, A_2 and Y_2 (previously these were called "prognostic factors"). Figure 1.1 postulates that U_0 cannot act as a direct cause of A_1 and A_2, but only as an indirect cause through intermediates L_1 and L_2 respectively. This is therefore an assumption formulated through our causal DAG, which was previously already stated through SRA (1.9). The arrows from L_1 into L_2 and from A_1 into A_2 encode our understanding that factors of previous time-points causally affect the risk of these factors at the current time-point. The arrow from A_1 into L_2 points out that measured prognostic factors at $t = 2$ might be affected by exposure at $t = 1$. Note that L_2 has the property to act both as a common cause and as an intermediate variable of the exposure-outcome relations $A_2 - Y_2$ and $A_1 - Y_2$ respectively, the former meaning that it directly causes both A_2 and Y_2 and the latter that it is an intermediate variable in the causal path that leads from A_1 to Y_2. Finally, C_t at each time-point is only directly caused by earlier exposure and measured prognostic variables. Also here, U_0 is assumed to only cause C_t through L_t and A_t. This follows from ICA (1.12), guaranteeing that all paths that link C_t with Y_t pass through L_t or A_t. Furthermore, C_t and Y_t are assumed not to be causally related. Importantly, the C_t variable being surrounded by a square box indicates that it is conditioned on, ie. that our analysis is stratified on this variable. This is indicative of the fact that once a subject is lost to follow-up, no further information will be available, or that the analysis is restricted to subjects with $C_t = 0$.

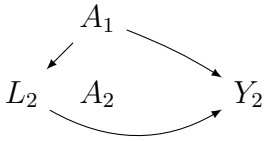
The causal effects of interest of Diagram 1.1 are shown in Figure 1.2 as isolated directed edges going from A_1 and A_2 into Y_2 . Subfigure 1.2a shows the *overall effect of* A_1 *on* Y_2, these are all directed edges from A_1 into Y_2. Subfigure 1.2b shows the *overall effect of* A_2 *on* Y_2, this is the single directed edge from A_2 into Y_2. Subfigure 1.2c shows the *direct effect of* A_1 *on* Y_2, this is the overall effect shown in Subfigure 1.2a minus directed edges from A_1 into Y_2 that pass through A_2. The different causal paths between A_1 and Y_2 and between A_2 and Y_2 signify that exposure might have a time-varying and cumulative effect, ie. that the effect of



(a) Overall effect of A_1.



(b) Overall effect of A_2.



(c) Controlled direct effect of A_1.

Figure 1.2: Causal paths between exposure A_1 and A_2, and outcome Y_2.

exposure at $t = 1$ on outcome could be different from and add to the effect at $t = 2$.

A causal DAG is linked to the full data distribution as follows. Letting $f(V) = f(V_1, ..., V_m)$ be the joint density of all variables in the diagram with m the number of variables, Pearl (2009) describes a causal DAG as having an underlying *nonparametric structural equation model*. In this model, each observed variable V_j is represented as the output of a nonparametric functional having as input its observed and unobserved parent variables. The latter are not explicitly accounted for but enter as error terms which are assumed to be jointly independent across functionals. *Parent variables* of V_j are those variables in the diagram having a

direct causal effect on V_j. In turn, V_k will be called a *descendant* of V_j if a causal path exists between V_j and V_k such that V_k can be reached by starting from V_j and following the direction of the arrows. Note that

$$f(V_1, ..., V_M) = \prod_{j=1}^{M} f(V_j|V_1, .., V_{j-1}) \tag{1.15}$$

which is denoted the *Chain rule*. Linking this to a causal DAG, we eliminate from the right part of above equation those variables that are independent of V_j conditional on its parents, such that

$$P(V_j|V_1, ..., V_{j-1}) = P(V_j|PA_j) \tag{1.16}$$

in which PA_j are the parent variables of V_j as postulated by the DAG. Equation (1.16) substituted in Chain rule (1.15) is called the *Causal Markov Assumption*. Using the study with $T_m = 2$ under the causal DAG of Figure 1.1 - without censoring variable C_t - the joint data distribution becomes

$$\begin{aligned} f(\overline{V}) &= f(Y_2|A_2, L_2, A_1, L_1, U_0)f(A_2|L_2, A_1, L_1)f(L_2|A_1, L_1, U_0) \\ &\quad \times f(A_1|L_1)f(L_1|U_0)f(U_0) \end{aligned} \tag{1.17}$$

The above description of $f(\overline{V})$ based on the variables and relations depicted in causal DAG of Figure 1.1 is needed to construct the distribution of counterfactual outcomes. We will use this distribution to identify our causal contrasts of interest. The counterfactual variables generated under an intervention "set exposure regime (A_1, A_2) to level (a_1, a_2)" can be visualised in the causal DAG by replacing exposure variables (A_1, A_2) by (a_1, a_2), and their descendant variables V_k by $V_{k,(a_1,a_2)}$, or the counterfactual variables under exposure regime (a_1, a_2). This intervention will also remove all ingoing edges into (A_1, A_2) from the diagram. Consider then $f\{\overline{V}_{2,(a_1,a_2)}\}$ or the counterfactual joint data distribution under exposure regime $(A_1, A_2) = (a_1, a_2)$:

$$f\{\overline{V}_{2,(a_1,a_2)}\} = f\{Y_{2,(a_1,a_2)}|a_2, L_{2,(a_1,a_2)}, a_1, L_1, U_0\}f\{L_{2,(a_1,a_2)}|a_1, L_1, U_0\}$$

$$\begin{aligned} & \times f(L_1|U_0)f(U_0) \\ = \; & f(Y_2|a_2, L_2, a_1, L_1, U_0)f(L_2|a_1, L_1, U_0)f(L_1|U_0)f(U_0) \end{aligned} \quad (1.18)$$

the first equality of which is based on setting the conditional distribution functions $f(A_2|L_2, A_1, L_1, U_0)$ and $f(A_1|L_1, U_0)$ to 1 once exposure regime (A_1, A_2) is set or fixed to a particular exposure regime (a_1, a_2). Setting counterfactuals through intervening on an exposure regime under causal Markov assumption (1.16) is called *Truncated factorisation*. The last equality of (1.18) is due to consistency of exposure regime, and is a next step in the identification of causal effects. We will continue this in Section 1.4, but will first demonstrate how to use causal DAGs to detect confounding of the exposure-outcome relationship as well as selection bias.

1.3.7 Bias classification

One can now use the causal DAG of Figure 1.1 to verify whether the association between A and Y is confounded. This happens by inspecting the paths between A_2 (A_1) and Y_2 that do not allow starting in A_2 (A_1) and ending in Y_2 by following the direction of the arrows along the considered path. These are called non-causal paths because any association between A_2 (A_1) and Y_2 by means of such pathway in the diagram will not reflect causation, and may hence signal *confounding of the exposure-outcome relationship*. Not all non-causal paths will however induce non-causal association (Robins and Morgenstern, 1987; Vanderweele and Shpitser, 2013). To determine whether a non-causal path in the diagram may actually induce association between exposure and outcome, in which case we call it an "open path" (as opposed to a "blocked path"), we will rely on 3 rules derived from causal DAG theory (Pearl, 1995). In these rules, a variable is a *collider* in a path if two arrowheads in the path point into (or collide at) this variable. Also, we consider the analysis to *condition on* a variable when the analysis stratifies on the values of this variable; this is depicted on the causal diagram by a square around the conditioned variable.

1 Any path containing a non-collider that has been conditioned on is blocked.

2 A path containing no conditioned variables is blocked if it contains a collider.

3 Conditioning on a colliding variable or on one of its descendants will open the path's section passing through that variable.

Using the causal DAG of Figure 1.1, we will discuss non-causal paths that link A_2 (A_1) with Y_2, look for each if it actually creates non-causal association, and see how it can be resolved in an analysis. Without any adjustment for the effect of exposure on outcome by prognostic variables U_0 and/or L at $t = 1$ or $t = 2$, this is seen as a *crude analysis* of the effect of joint exposure (A_1, A_2) on the mean of Y_2. The diagrams depicted in Figures 1.3 and 1.4 have been created by investigating and classifying all possible non-causal paths between A_1 and Y_2 and between A_2 and Y_2 respectively that are not blocked according to rules 1-3, we will call these *open non-causal paths*. Neither diagram depicted in Figures 1.3 and 1.4 can be considered causal or linked to the data of our study since only part of variables and their causal relations are shown each time.

For example, the diagram of Subfigure 1.3a identifies the following 4 paths between A_1 and Y_2:

$$A_1 \leftarrow L_1 \rightarrow Y_2 \tag{1.19}$$

$$A_1 \leftarrow L_1 \leftarrow U_0 \rightarrow Y_2 \tag{1.20}$$

$$A_1 \rightarrow \boxed{C_1} \leftarrow L_1 \rightarrow Y_2 \tag{1.21}$$

$$A_1 \rightarrow \boxed{C_1} \leftarrow L_1 \leftarrow U_0 \rightarrow Y_2 \tag{1.22}$$

All these paths are non-causal because, by following the direction of the arrows in these paths, A_1 can never lead to Y_2. Following rules 1 and 2, paths (1.19) and (1.20) are open because they do not contain colliders or conditioned variables. These paths will therefore lead to confounding of the $A_1 - Y_2$ relationship.

For example, letting L_1 indicate exposure to mechanical ventilation, the fact that L_1 is a causal risk factor for both A_1 (being exposed to mechanical ventilation increases the risk for acquiring infection, following the aforementioned example) and Y_2 (being exposed to mechanical ventilation is an effect of a worse prognosis, and thus increases the risk of dying) will create a positive association between A_1

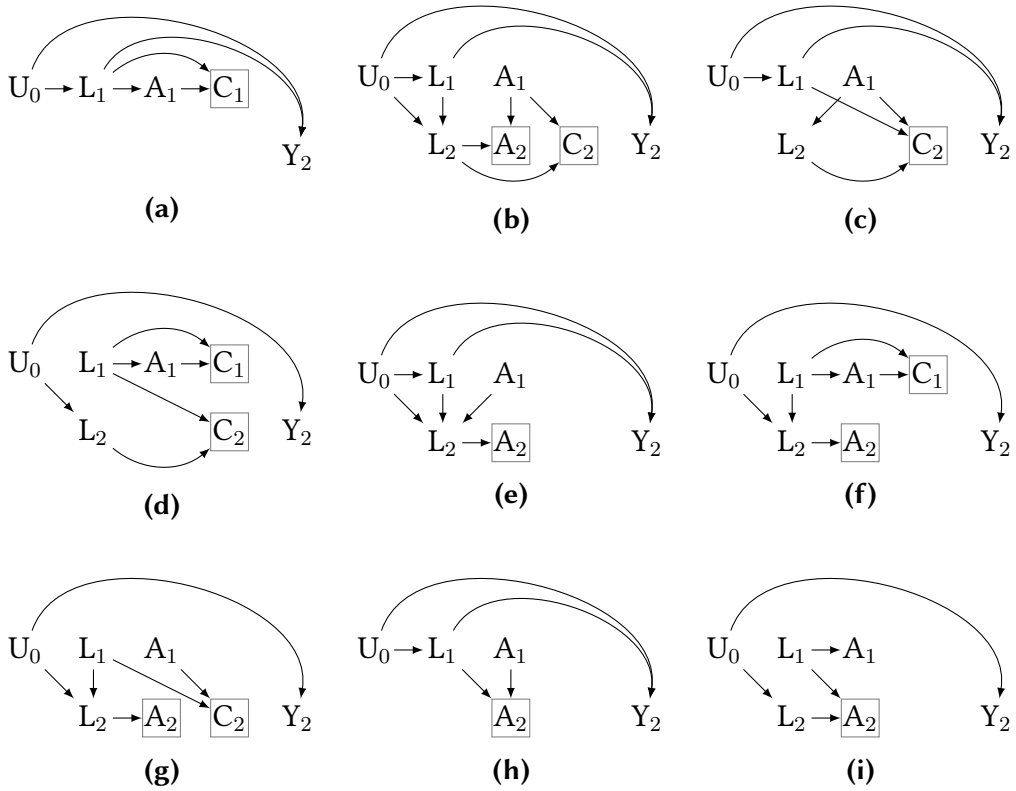


Figure 1.3: Non-causal open paths between A_1 and Y_2, in an unadjusted analysis of the joint effect of (A_1, A_2) on Y_2.

and Y_2 through L_2, even in the absence of a causal effect of A_1 on Y_2.

For paths (1.21) and (1.22) passing through variable C_1, recall that our data is restricted to subjects under follow-up, meaning that the analysis is conditional on $C_1 = 0$. Variable C_1 acts as a collider in these paths, and is conditioned on, implying that according to rule 3, the section in paths (1.21) and (1.22) from A_1 until L_1 will be open. Because the remaining sections of these paths until Y_2 are equal to open paths (1.19) and (1.20), we conclude that paths (1.21) and (1.22) are also open paths. The phenomenon when conditioning on a common effect of two variables leads to a spurious or non-causal association between these variables is called *collider-stratification bias*. In this case it is also referred to as *informative censoring* or *selection bias* because censoring is associated with both the outcome (through L_2 and U_0) as with exposure, and through conditioning on C_1 a sample is created that is selective with respect to these prognostic factors (ie. not representative of the source population) (Hernàn et al., 2004; Daniel et al., 2012). Such selection bias may occur independently from the bias through confounding of the $A - Y$ relation via non-causal paths (1.19) and (1.20).

Such bias can be intuitively understood by the following example. Suppose that $U_0 = 1$ leads to $L_2 = 1$ and $Y_2 = 1$, that $L_2 = 1$ leads to $A_2 = 1$, $Y_2 = 1$, $C_2 = 0$, and that $A_2 = 1$ leads to $C_2 = 0$. Assume also the null hypothesis of no effect of exposure on outcome. Then even so, by selecting subjects under follow-up (i.e. having $C_2 = 0$), we will get the impression that exposure is negatively associated with outcome because those unexposed ($A_2 = 0$) will likely have $L_2 = 1$ and thus have a worse prognoses ($U_0 = 1$ and $Y_2 = 1$), since the cause why they remain under follow-up is not due to the absence of exposure. Similarly, those subjects that are in a better condition ($U_0 = 0$ and $L_2 = 0$) will likely be exposed ($A_2 = 1$), since the cause why they remain under follow-up is not the fact that $L_2 = 1$. Thus, in the group of $C_2 = 0$, there is a negative association between A_2 and U_0. Because U_0 is associated with Y_2, this means a negative association between A_2 and Y_2 is expected after conditioning on $C_2 = 0$.

Non-causal paths of Subfigures 1.3e, 1.3f and 1.3g all show A_2 as a conditioned descending variable of L_2. Such conditioning on A_2 occurs because an analysis for the unadjusted joint effect will measure the effect of both variables A_1 and

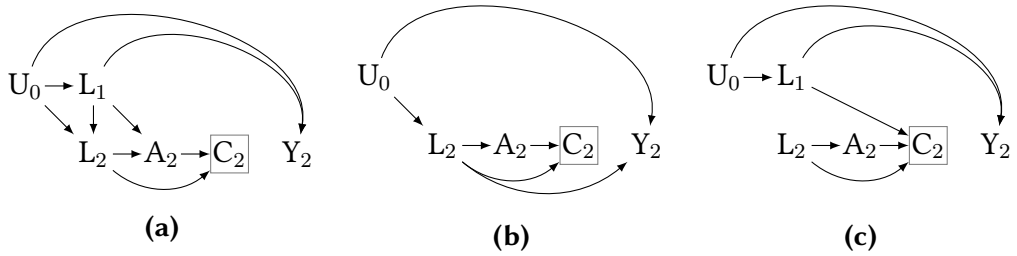


Figure 1.4: Non-causal open paths between A_2 and Y_2, in an unadjusted analysis of the joint effect of (A_1, A_2) on Y_2.

A_2 simultaneously, therefore the effect of A_1 on the risk of Y_2 will be conditioned on the values of A_2. According to rule 3, these paths will all be opened by this and hence create non-causal associations between A_1 and Y_2 (Robins and Hernàn, 2009). Finally, in non-causal paths of Subfigures 1.3b and 1.3h-1.3i, A_2 acts as a collider that is conditioned on, which open these non-causal paths by rule 3.

Figure 1.4 isolates non-causal open paths between variables A_2 and Y_2 in an unadjusted analysis of the joint effect of (A_1, A_2) on Y_2. The three types of open non-causal paths of Subfigures 1.4a-1.4c are all due to variables U_0, L_1 and L_2 acting as confounders of the causal effect of A_2 on Y_2. Also, this effect will suffer from the same conditioning on the C_2 variable and inherent selection bias as with C_1.

1.3.8 Time-dependent confounding

It is common practice in statistical analysis to eliminate confounding of the exposure-outcome relationship (like the one described above) by conditioning on the common cause (e.g. U_0 or L_t) of exposure and outcome. This means that the association between exposure and outcome will be calculated within strata of the common cause. Because all subjects within a stratum are similar in terms of this common cause, this will eliminate the association between the common cause and its effects within each stratum. This is what is meant by rule 1 of causal diagram theory, when blocking a non-causal path between two variables (eliminating spurious association) by conditioning on a non-collider. The same arguments apply

when correcting for selection bias by informative censoring: spurious associations between censoring and outcome can be avoided by stratifying or conditioning on common causes of the censoring and outcome variable.

The idea is therefore to find variables that can be used to block the open non-causal paths in Figures 1.3 and 1.4 between A_1 and Y_2 and between A_2 and Y_2 respectively, but without opening blocked paths. In order to block non-causal paths of our causal DAG, conditioning on U_0 is impossible as it is unmeasured and not available for use in the analysis, which leaves us to work with variables L_1 and L_2. Figures 1.5 and 1.6 shows non-causal open paths of Figures 1.3 and 1.4 respectively, but with L_1 and L_2 variables conditioned on, visible by a square around these variables. Conditioning on L_1 will block open non-causal paths between A_1 and Y_2 of Subfigures 1.3a-1.3d, while conditioning on L_2 will also block remaining open paths between A_1 and Y_2 of Subfigure 1.3b. Conditioning on L_1 and/or L_2 will also block paths of Subfigures 1.3h-1.3i that were originally opened because A_2 was conditioned on. Also, conditioning on L_1 and/or L_2 will block open non-causal paths between A_2 and Y_2 of Subfigures 1.4a-1.4c.

We succeeded in blocking above non-causal paths even though U_0 is unmeasured. This is due to SRA (1.9), under which each causal effect of U_0 on A_1 or A_2 must pass through variables L_1 or L_2. Without this assumption, U_0 would have direct causal effects on A_1 or A_2, and no measured variables would be available for adjustment. The same argument applies for ICA (1.12), or that U_0 only affects censoring variables C_1 and C_2 through measured confounders L_1, L_2.

Focus now on non-causal paths between A_1 and Y_2 in which L_2 acts as a collider, more specifically paths in Subfigures 1.3e-1.3g. Originally, these paths were all opened due to L_2 acting as collider with the descendant A_2 in these paths being conditioned on. Conditioning on L_1 and L_2 will block all paths except for the one passing through the $U_0 \to L_2$ section in Subfigure 1.3e. This is because the direct effect of U_0 on L_2 offers no possibility to block this path by means of a measured common cause. In summary, we used causal diagram rule 1 to block open non-causal paths between A_1 and Y_2, and between A_2 and Y_2, and rules 2 and 3 to demonstrate that particular blocked non-causal paths will be opened by conditioning on L_2. In this case, collider-stratification or selection bias is created

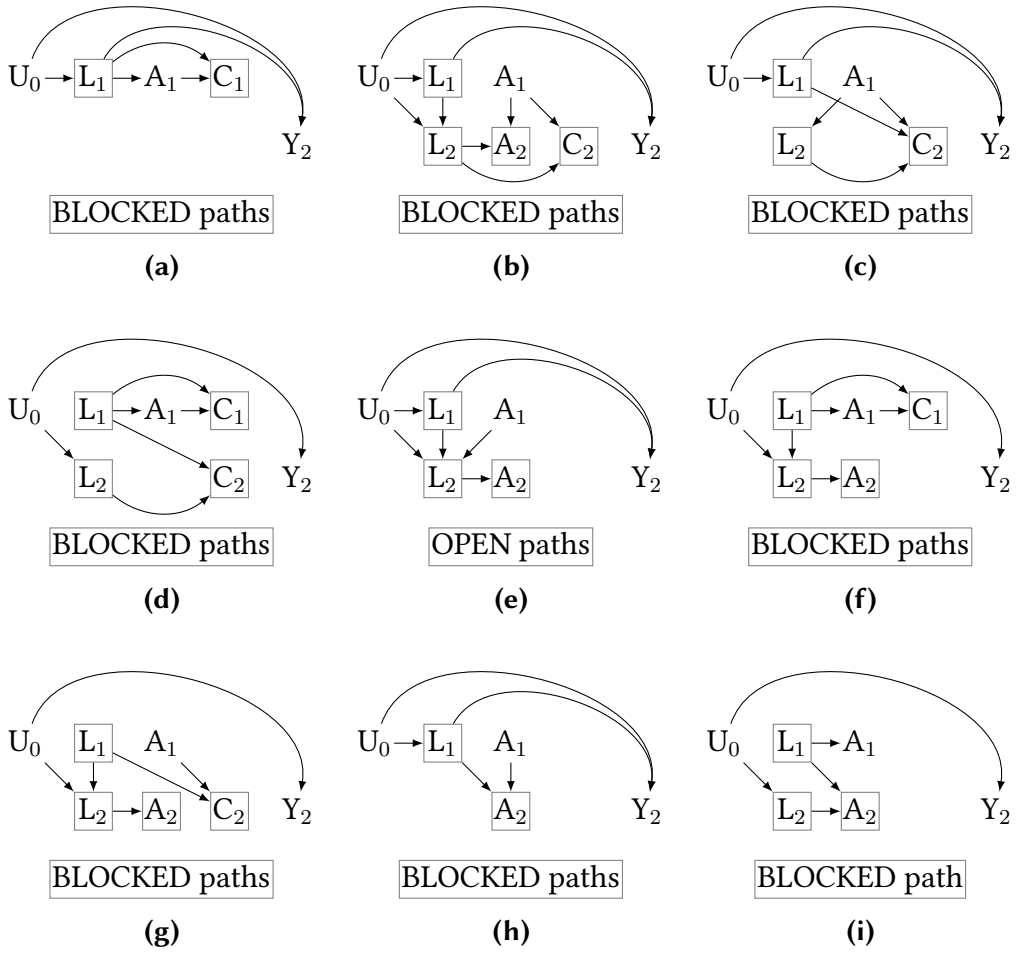


Figure 1.5: Non-causal paths between exposure A_1 and outcome Y_2, in an adjusted analysis of the joint effect of (A_1, A_2) on Y_2, when stratifying for prognostic variables L_1 and L_2.

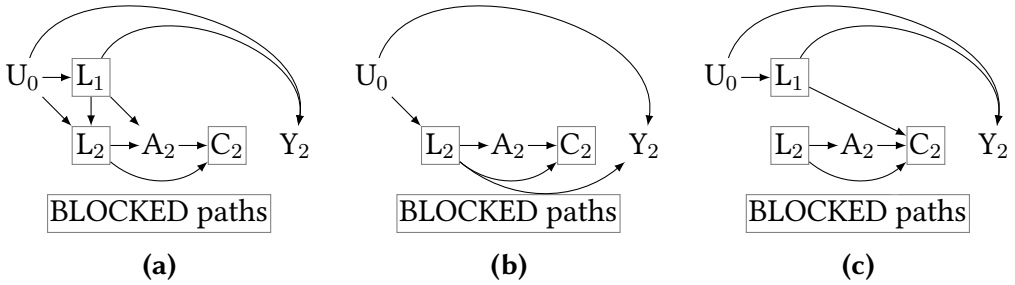


Figure 1.6: Non-causal paths between exposure A_2 and outcome Y_2, in an adjusted analysis of the joint effect of (A_1, A_2) on Y_2, when stratifying for prognostic variables L_1 and L_2.

by conditioning on L_2 which acts as a collider in non-causal path $U_0 \rightarrow L_2 \leftarrow A_1$. Here, it will lead to *time-dependent confounding* of the exposure-outcome relation, so-called because it is induced by conditioning on the time-dependent confounder L_2. In the presence of such confounding, stratification-based regression methods for Y_2 that adjust for confounders acting both as cause and effect of exposure may yield biased effect estimates (Hernàn et al., 2004; Robins and Hernàn, 2009; Daniel et al., 2013). We will elaborate on this in the next section. Avoiding adjusting for L_2 by only conditioning on confounders L_1 (occurring before the onset of A_1) does not remedy this problem because then particular non-causal paths between A_2 and Y_2 that pass through L_2 will remain open. All stratification-based methods that analyse the effect of exposure to infection on ICU-mortality will suffer from this problem of adjustment for time-dependent confounding: while adjustment is necessary to remove time-dependent confounding, ordinary stratification will induce selection bias.

Also, besides leading to time-dependent confounding, conditioning on the L_2 variable will be problematic when estimating the overall causal effect of A_1 on Y_2. As seen in the diagram of Subfigure 1.2a, part of this effect is mediated by L_2, therefore conditioning on L_2 will block part of the causal paths between A_1 and Y_2.

1.3.9 Stratified models for the joint effect of exposure

While a causal DAG encodes an underlying nonparametric model for counterfactuals, in practice we will not be able to model the mean of Y_t nonparametrically using a dataset with moderate sample size and many time-points, exposure regimes $\overline{a}$ and multi-dimensional time-dependent confounders L_t. Therefore, we return to the example of section 1.3.3 where we relied on a parametric regression model for the discrete-time hazard of counterfactual outcome $Y_{t,\overline{a}}$ at $t \leq 2$. The DAG's causal effects represented in Subfigures 1.2a, 1.2b and 1.2c will correspond with aforementioned contrasts $\exp(\beta_1^{c,1})$, $\exp(\beta_2^{c,1})$ and $\exp(\beta_1^{c,1} - \beta_2^{c,1})$ respectively that were derived from model (1.7). Because this example relies on the unrealistic situation where we could model an original dataset containing counterfactual outcomes for all exposure regimes, we will now verify if we can obtain causal contrasts by modelling observed data. In doing so, we will ignore the problems linked to the causal interpretation of the hazard ratio that we explained in Section 1.3.3, as these can be resolved by conversion towards the survival risk ratio using (1.5).

First, consider the pooled logistic regression model derived from earlier model (1.1):

$$\begin{aligned} P(Y_t = 1 | Y_{t-1} = 0, (a_1, a_2); \beta^{cr}) &= \text{expit}\{\beta_0^{cr} + \beta_1^{cr} a_1 + \beta_2^{cr} a_2 (1 - a_1)\} \\ &\quad \text{at } t \leq 2 \end{aligned} \tag{1.23}$$

with unknown parameter β^{cr}, so-called because it estimates a crude effect, due to no adjustment being made for confounders of the exposure-outcome relation. Therefore, it will generally fail in delivering causal estimates of the effect of exposure on outcome. To see this, consider the contrast estimated by β_1^{cr}:

$$\begin{aligned} \exp \beta_1^{cr} &= \frac{P\{Y_t = 1 | \overline{Y}_{t-1}, (a_1, a_2) = (1,1); \beta^{cr}\}}{P\{Y_t = 1 | \overline{Y}_{t-1}, (a_1, a_2) = (0,0); \beta^{cr}\}} \\ &= \frac{P\{Y_{t,(1,1)} = 1 | \overline{Y}_{t-1,(1,1)}, (a_1, a_2) = (1,1); \beta^{cr}\}}{P\{Y_{t,(0,0)} = 1 | \overline{Y}_{t-1,(0,0)}, (a_1, a_2) = (0,0); \beta^{cr}\}} \\ &\quad \text{at } t \leq 2 \end{aligned} \tag{1.24}$$

or the relative risk for the outcome of subjects under exposure regime $(a_1, a_2) = (1, 1)$ versus $(0, 0)$ at $t \leq 2$. In order to interpret this as a causal contrast, we use Consistency assumption (1.8) in the second line of (1.24) to present the numerator and denominator as means of a counterfactual outcome. Next, we need to turn the conditional mean for each counterfactual into a population mean, however we will fail in doing so because SRA (1.9) only defines independence between $Y_{t,\overline{a}}$ and A_t *conditional on* confounder history $\overline{L}_t$, which is a variable lacking from regression model (1.23). Therefore, contrast (1.24) uses means of counterfactuals that are defined within different subgroups [$\overline{a} = (1, 1)$ versus $\overline{a} = (0, 0)$] that are not exchangeable in terms of prognostic factors U and L. This contrast will thus be biased due to confounding by U and/or L. A same reasoning applies for the contrast that compares exposure regime $(a_1, a_2) = (0, 1)$ with $(0, 0)$ at $t = 2$.

Now consider models for the stratified effect of exposure. A causal diagram adapted towards a conditioned L_t variable represents such a stratified analysis, ie. by calculating the joint effect of exposure at $t - 1$ and t on outcome at t by using observations for which $C_t = 0$ and stratified for L_t. Table 1.1 shows the identification of causal contrasts under SRA (1.9) using a stratified pooled logistic regression model for the discrete-time hazard of Y_t: $P(Y_t = 1|Y_{t-1} = 0, \overline{V}; \beta^s) = \text{expit}\{\beta^{s'} V\}$ at $t \leq 2$. This uses the unknown parameter vector β^s ("s" for stratified), with the following model parametrisations for $\beta^{s'} V$:

$$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1 - a_1) + \beta_3^s L_1 + \beta_4^s L_2 \tag{1.25}$$

$$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1 - a_1) + \beta_3^s L_1 \tag{1.26}$$

$$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1 - a_1) + \beta_3^s L_1 + \beta_4^s L_2(1 - a_1) \tag{1.27}$$

Model (1.25) stratifies the effect of joint exposure for L_1 and L_2, model (1.26) stratifies for L_1 only, and model (1.27) stratifies for L_1 and L_2 under $(a_1, a_2) = \{(0, 0), (0, 1)\}$ and for L_1 under $(a_1, a_2) = (1, 1)$. Note that we use a monotonous exposure where only the onset of exposure is set randomly conditionally on exposure and covariate history, and deterministically (to 1) once onset occurred. Under such monotonous exposure, the use of SRA will be limited to only one time-point when identifying the conditional average of the counterfactual outcome under

exposure regimes $(1,1)$. This is shown as follows for stratified model (1.25):

$$\begin{aligned}
&P\{Y_t = 1|Y_{t-1} = 0, (a_1, a_2) = (1,1), \overline{L}_2\} \\
&= P\{Y_t = 1|Y_{t-1} = 0, a_1 = 1, a_2 = 1, L_1, L_2\} \\
&= P\{Y_t = 1|Y_{t-1} = 0, a_1 = 1, L_1, L_2\} \\
&= P\{Y_{t,(1,1)} = 1|Y_{t-1,(1,1)} = 0, a_1 = 1, L_1, L_{2,(1,1)}\} \\
&= P\{Y_{t,(1,1)} = 1|Y_{t-1,(1,1)} = 0, L_1, L_{2,(1,1)}\} \qquad (1.28)
\end{aligned}$$

with the second equality due to monotonous exposure, the third to consistency of exposure regime, and the fourth to SRA at $t = 1$. Similarly, we can derive the conditional average of the counterfactual outcome under exposure regime $(0,0)$ as follows

$$\begin{aligned}
&P\{Y_t = 1|Y_{t-1} = 0, (a_1, a_2) = (0,0), \overline{L}_2\} \\
&= P\{Y_t = 1|Y_{t-1} = 0, a_1 = 0, a_2 = 0, L_1, L_2\} \\
&= P\{Y_t = 1|Y_{t-1} = 0, a_2 = 0, L_1, L_2\} \\
&= P\{Y_{t,(0,0)} = 1|Y_{t-1,(0,0)} = 0, a_2 = 0, L_1, L_{2,(0,0)}\} \\
&= P\{Y_{t,(0,0)} = 1|Y_{t-1,(0,0)} = 0, L_1, L_{2,(0,0)}\} \qquad (1.29)
\end{aligned}$$

with the second equality due to monotonous exposure, the third to consistency of exposure regime, and the fourth to SRA at $t = 2$.

Table 1.1 shows that none of the stratified models succeed in delivering joint causal contrasts. This is due to all regression models failing to identify a valid causal contrast between exposure regimes $(a_1, a_2) = (1,1)$ and $(0,0)$ at $t = 2$. Interestingly, the models and types of exposure that are able to identify averages of counterfactual outcomes in both numerator and denominator, still fail in identifying a causal contrast because the counterfactual means are defined within different subgroups. For example, model (1.25) in the 1st line of Table 1.1 compares a counterfactual mean defined within subgroup $L_{2,(1,a_2)}$ with a counterfactual mean defined within subgroup $L_{2,(0,a_2)}$. Counterfactual variable $L_{t,\overline{a}}$ is here defined as L_t under exposure regime set to $\overline{a}$. Because stratification for L_2 in a regression model based on (1.25) will force the subgroups defined by $L_{2,\overline{a}}$ to be equal, this will lead

to the time-dependent confounding described in the previous section. Model (1.27) only partially corrects for this, in that the denominator's counterfactual mean is still defined within subgroup $L_{2,(0,a_2)}$, which is different from the numerator.

In contrast to this, some models do succeed in identifying the causal contrast between exposure regimes $(a_1, a_2) = (0, 1)$ and $(0, 0)$. As shown in the second part of Table 1.1, this is the case for models (1.25) and (1.27), where contrasts have a causal interpretation not only because of successful identification of averages of counterfactual outcomes in both numerator and denominator, but also because these are defined within the same subgroup. Note however that contrasts are defined as conditional contrasts, and that for this reason, they may not be equal to the earlier defined *marginal contrast*, for example see parameter $\exp \beta_2^c$ in model (1.7) for the effect of exposure regime $(a_1, a_2) = (0, 1)$ versus $(0, 0)$.

It might be insightful to verify whether we can use stratified regression models to estimate the *aggregated overall causal effect of exposure*, like we did earlier using model (1.3). In such a stratified model, the coefficients β_1^s and β_2^s will be aggregated into one coefficient, using a parametrisation such as

$$\beta_0^{sa} + \beta_1^{sa} a_2 + \beta_2^{sa} L_1 + \beta_2^{sa} L_2 (1 - a_1) \tag{1.30}$$

in which coefficient β_1^{sa} will now encode the effect of either exposure regime $(a_1, a_2) = (0, 1)$ or $(1, 1)$ versus exposure regime $(0, 0)$, and which will be adjusted for L_1 and/or L_2 depending on exposure status at the first time-point. Because β_1^{sa} now summarises the earlier two exposure effects into one, for which we showed that one (the β_1^s coefficient in models 1.25-1.27) cannot lead to a causal contrast, we conclude that the parameter β_1^{sa} will not identify a causal contrast either. Therefore, stratified regression models will also be unable to provide estimates of aggregated causal effects.

If we consider a point-treatment study with $T_m = 1$, we can use the results of the previous paragraphs to identify a valid causal contrast between exposure $a = 1$ and 0. To do so, we need to ignore all variables at $t = 2$, after which models (1.25-1.27) will be equal, and $\exp \beta_1^s$ can be shown to estimate a valid causal contrast $P(Y_{1,a_1=1}|L_1)/P(Y_{1,a_1=0}|L_1)$. This shows that, under conditional randomisation in

$V\beta^{s'}$	Identification of exposure effect	
Exposure regime $(1,1)$ *versus* $(0,0)$		
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s L_2$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(1,1),\overline{L}_2\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),\overline{L}_2\}}$	$= \frac{P\{Y_{t,(1,1)}=1\|Y_{t-1,(1,1)}=0,L_1,L_{2,(1,a_2)}\}}{P\{Y_{t,(0,0)}=1\|Y_{t-1,(0,0)}=0,L_1,L_{2,(0,a_2)}\}}$
		$= \exp\beta_1^s$
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(1,1),L_1\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),L_1\}}$	$= \frac{P\{Y_{t,(1,1)}=1\|Y_{t-1,(1,1)}=0,L_1\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),L_1\}}$
		$= \exp\beta_1^s$
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s L_2(1-a_1)$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(1,1),L_1\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),\overline{L}_2\}}$	$= \frac{P\{Y_{t,(1,1)}=1\|Y_{t-1,(1,1)}=0,L_1\}}{P\{Y_{t,(0,0)}=1\|Y_{t-1,(0,0)}=0,L_1,L_{2,(0,a_2)}\}}$
		$= \exp(\beta_1^s - \beta_4^s)$
Exposure regime $(0,1)$ *versus* $(0,0)$		
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s L_2$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,1),\overline{L}_2\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),\overline{L}_2\}}$	$= \frac{P\{Y_{t,(0,1)}=1\|Y_{t-1,(0,1)}=0,L_1,L_{2,(0,a_2)}\}}{P\{Y_{t,(0,0)}=1\|Y_{t-1,(0,0)}=0,L_1,L_{2,(0,a_2)}\}}$
		$= \exp\beta_2^s$
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,1),L_1\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),L_1\}}$	$= \exp\beta_2^s$
$\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s L_2(1-a_1)$	$\frac{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,1),\overline{L}_2\}}{P\{Y_t=1\|Y_{t-1}=0,(a_1,a_2)=(0,0),\overline{L}_2\}}$	$= \frac{P\{Y_{t,(0,1)}=1\|Y_{t-1,(0,1)}=0,L_1,L_{2,(0,a_2)}\}}{P\{Y_{t,(0,0)}=1\|Y_{t-1,(0,0)}=0,L_1,L_{2,(0,a_2)}\}}$
		$= \exp\beta_2^s$

Table 1.1: Derivation of joint population contrasts under sequential randomisation* and using different stratified regression models** for the joint effect of a time-dependent monotonous exposure regime (a_1, a_2) on the discrete-time hazard of a binary Y_t in a study with 2 time-points; *using $Y_{t,\overline{a}} \amalg A_s | Y_{s-1} = 0, A_{s-1} = a_{s-1}, \overline{L}_s$ for all $t, s \leq t$; **using logistic regression to model the discrete-time hazard as in: $P\{Y_t = 1 | Y_{t-1} = 0, V_t; \beta^s\} = \text{expit}(V_t\beta^{s'})$ with $\text{expit}(u) = \exp(u)/\{1+\exp(u)\} \equiv \exp(u)$ under a rare outcome.

a point-treatment study, stratification will be sufficient in identifying a conditional contrast for the causal effect of exposure. However, in a longitudinal study where the objective is to estimate the effect of time-varying exposures in the presence of time-dependent prognostic factors acting as both cause and effect of exposure, stratification will fail in identifying the causal contrast between exposure regimes $(a_1, a_2) = (1, 1)$ and $(0, 0)$. Therefore, it will also fail to identify the causal contrasts between exposure regimes $(a_1, 1)$ and $(0, 0)$ (the aggregated overall effect of exposure) and between exposure regimes $(1, 1)$ and $(0, 1)$ (earlier described as the controlled direct effect of exposure at $t = 1$ on outcome at $t = 2$). We conclude that, despite the simplicity that lies in the use of stratified regression models to eliminate confounding, stratification under such models will only be able to estimate parameters that measure associations between time-varying exposures and outcomes, instead of causal effects.

1.4 Estimators of joint causal effects

1.4.1 G-computation

Our objective is to identify the average of $Y_{2,\bar{a}}$, thereby avoiding the pitfalls described in the previous section. We will try to find ways in which this average can be identified from earlier derived counterfactual density $f(\overline{V}_{2,\bar{a}})$ (1.18). The density $f(Y_{2,\bar{a}})$ for the counterfactual $Y_{2,\bar{a}}$ is obtained by summing (1.18) over all realisations of variables in set $\overline{V}_2 \setminus (A_2, A_1, Y_2)$ as in

$$\begin{aligned} \sum_{U_0,L_1,L_2} f\left\{(U_0, L_1, a_1, L_2, a_2, Y_2)_{(a_1,a_2)}\right\} &= f\left\{(Y_2, a_2, a_1)_{(a_1,a_2)}\right\} \\ &= f(Y_{2,(a_1,a_2)}) \end{aligned} \tag{1.31}$$

in which we assume categorical (U_0, L_1, L_2) for simplicity, and similarly for the right-hand side of the last line of (1.18)

$$f\{Y_{2,(a_1,a_2)}\} = \sum_{U_0,L_1,L_2} f(Y_2|a_2, a_1, L_1, L_2, U_0) f(L_2|a_1, L_1, U_0)$$

$$\times f(L_1, U_0) \tag{1.32}$$

which is the standardisation procedure of equation (1.11) but applied to causal DAG of Figure 1.1. Because (1.32) relies on parent variables of Y_2, which includes the unmeasured U_0, this will be of no practical use for identification of the mean of $Y_{2,(a_1,a_2)}$. Making use of the assumptions encoded by the causal DAG of Figure (1.1) (Daniel et al., 2013), we obtain

$$\begin{aligned}
f\{Y_{2,(a_1,a_2)}\} &= \sum_{U_0,L_1,L_2} f(Y_2|a_2,a_1,L_2,L_1,U_0) f(L_2|a_1,L_1,U_0) f(L_1,U_0) \\
&= \sum_{U_0,L_1,L_2} f(Y_2|a_2,a_1,L_2,L_1,U_0) f(L_2|a_1,L_1,U_0) f(L_1,U_0) \\
&\quad \times \frac{f(A_2=a_2|L_2,a_1,L_1,U_0) f(A_1=a_1|L_1,U_0)}{f(A_2=a_2|L_2,a_1,L_1,U_0) f(A_1=a_1|L_1,U_0)} \\
&= \sum_{U_0,L_1,L_2} f(Y_2|a_2,a_1,L_2,L_1,U_0) \\
&\quad \times \frac{f(a_2,L_2,a_1,L_1,U_0)}{f(A_2=a_2|L_2,a_1,L_1,U_0) f(A_1=a_1|L_1,U_0)} \\
&= \sum_{U_0,L_1,L_2} f(Y_2|a_2,a_1,L_2,L_1,U_0) \\
&\quad \times f(U_0|a_2,L_2,a_1,L_1) f(L_2|a_1,L_1) \\
&\quad \times \frac{f(A_2=a_2|L_2,a_1,L_1) f(A_1=a_1|L_1)}{f(A_2=a_2|a_1,L_2,L_1,U_0) f(A_1=a_1|L_1,U_0)} f(L_1) \\
&= \sum_{L_1,L_2} \left\{ \sum_{U_0} f(Y_2|a_2,a_1,L_2,L_1,U_0) f(U_0|a_2,L_2,a_1,L_1) \right\} \\
&\quad \times f(L_2|a_1,L_1) f(L_1) \\
&= \sum_{L_1,L_2} f(Y_2|a_2,a_1,L_2,L_1) f(L_2|a_1,L_1) f(L_1) \\
&\quad \text{if } (A_1,A_2) = (a_1,a_2)
\end{aligned} \tag{1.33}$$

In the above derivation, more specifically in the fourth equality, we use SRA (1.9), by which

$$f(A_2 = a_2|a_1, L_2, L_1, U_0) \quad = \quad f(A_2 = a_2|a_1, L_2, L_1)$$

$$f(A_1 = a_1|L_1, U_0) \quad = \quad f(A_1 = a_1|L_1) \tag{1.34}$$

Equation (1.33) is a time-dependent generalisation of standardisation procedure (1.11) to identify potential outcomes under time-dependent exposure regimes, and is called the *G-computation formula* (Robins, 1986; Robins and Hernàn, 2009; Daniel et al., 2013). G-computation has been shown to be a valid technique to identify joint causal effects in nonparametric settings. However, with high-dimensional L and moderate sample sizes, insufficient data will be available to allow separate estimation of the distributions for $f(Y_t|\overline{Y}_{t-1}, \overline{a}, \overline{L}_t)$ and $f(L_t|a_{t-1}, L_{t-1})$. Therefore, parametric modelling will be needed to estimate these quantities, with possible misspecification bounded to occur in the presence of high-dimensional L. Furthermore, Robins (1997) has shown that it is generally not feasible to postulate nonlinear models for Y_t and L_t that allow for both specification of the null hypothesis of no joint exposure effect and for intermediate confounding by L_t, leading to false rejection of the causal null hypothesis when it is true. This is known as the *null paradox of the estimated G-formula*.

For example, consider logistic regression models $P\{Y_t = 1|Y_{t-1} = 0, (a_1, a_2), \overline{L}_2; \beta^s\}$ based on model parametrisation (1.25) for the discrete-time hazard of Y_t and $P(L_2 = 1|a_1; \alpha) = \text{expit}(\alpha_0 + \alpha_1 a_1)$ for the conditional mean of a binary L_2. Using both models in G-computation formula (1.33) will give a model for the discrete-time counterfactual hazard as follows

$$\begin{aligned}
& P\{Y_{t,(a_1,a_2)} = 1|Y_{t-1,(a_1,a_2)} = 0, L_1; \beta^s\} \\
= \; & \exp\{\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s\}\text{expit}(\alpha_0 + \alpha_1 a_1) \\
& + \exp\{\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1\}\{1 - \text{expit}(\alpha_0 + \alpha_1 a_1)\} \\
= \; & \big[\exp\{\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1 + \beta_4^s + \alpha_0 + \alpha_1 a_1\} \\
& + \exp\{\beta_0^s + \beta_1^s a_1 + \beta_2^s a_2(1-a_1) + \beta_3^s L_1\}\big] \\
& \times \frac{1}{1 + \exp(\alpha_0 + \alpha_1 a_1)}
\end{aligned} \tag{1.35}$$

in which the direct effect of A_1 will be estimated by following contrast of counter-

factual hazards for exposure regime $(a_1, a_2) = (1, 1)$ versus $(0, 1)$:

$$\begin{aligned} & \frac{\exp(\beta_0^s + \beta_1^s + \beta_3^s + \beta_4^s + \alpha_0 + \alpha_1) + \exp(\beta_0^s + \beta_1^s + \beta_3^s)}{\exp(\beta_0^s + \beta_2^s + \beta_3^s + \beta_4^s + \alpha_0) + \exp(\beta_0^s + \beta_2^s + \beta_3^s)} \\ & \times \frac{1 + \exp(\alpha_0)}{1 + \exp(\alpha_0 + \alpha_1)} \\ = \quad & \frac{\exp(\beta_1^s)}{\exp(\beta_2^s)} \times \frac{1 + \exp(\beta_4^s + \alpha_0 + \alpha_1)}{1 + \exp(\beta_4^s + \alpha_0)} \times \frac{1 + \exp(\alpha_0)}{1 + \exp(\alpha_0 + \alpha_1)} \end{aligned} \tag{1.36}$$

It proves to be very difficult to find parameter realisations in which the null hypothesis of no direct effect of A_1 will hold, unless either $\beta_1^s - \beta_2^s = \alpha_1 = 0$ or $\beta_1^s - \beta_2^s = \beta_4^s = 0$. However, $\alpha_1 = 0$ would imply that A_1 has no causal effect on L_2, meaning absence of time-dependent confounding, while $\beta_4^s = 0$ would imply that A_2 and Y_2 are not confounded by L_2. Both these conditions are false under causal DAG of Figure 1.1. For reference, a null effect under a normally distributed L_2 variable that is modelled linearly with constant variance across exposure regimes would imply that $\beta_1^s - \beta_2^s + \beta_4^s \alpha_1 = 0$, which is feasible under scenarios other than setting $\beta_4^s = 0$ or $\alpha_1 = 0$, see Young and Tchetgen (2014) for details. Given these remarks, we will seek other methods for joint estimation of the causal effect of (A_1, A_2) on Y_t

1.4.2 Marginal structural proportional hazard models

Robins (1992, 2000) and colleagues propose *Marginal structural proportional hazards models (MSPHMs)* and *Structural nested accelerated failure time models (SNFTMs)* to estimate the attributable effect of a time-dependent exposure on a failure outcome in the presence of time-dependent confounders and informative censoring. We will introduce and illustrate MSPHMs here, and SNFTMs in the following section.

A MSPHM is a model for the marginal effect of exposure regime $\overline{a}$ on $\lambda_{Y_{\overline{a}}}$, the hazard of the counterfactual outcome Y under this exposure (Robins, 2000; Hernàn

et al., 2001), and have the form (discrete-time version)

$$P(Y_{t,\overline{a}} = 1 | Y_{t-1,\overline{a}} = 0, L_0; \beta^0) = \text{expit}\{\gamma_{\text{msm}}(\overline{a}_t, L_0; \beta^0)\} \tag{1.37}$$

$$\text{for all } \overline{a_t} \tag{1.38}$$

with γ_{msm} a known function and β^0 the (unknown) true parameter vector of interest that gives the causal effect of exposure on survival on the hazard scale. The term "marginal" implies that the hazard is calculated over the levels of $\overline{L}_t$, the measured time-dependent confounder history until t. Because model (1.37) allows to contrast the counterfactual hazard under exposure regime $\overline{a}$ with that same subject's counterfactual hazard under absence of exposure, parameter β^0 of the exposure effect $\overline{a}$ has a causal interpretation. For example, when $\gamma_{\text{msm}}\{(a_1, a_2), L_0; \beta^0\} = \beta_0^0 + \beta_1^0 a_1 + \beta_2^0 a_2(1 - a_1)$, then model (1.37) will be equal to earlier discussed model (1.7) that parametrised causal contrasts.

Informally, the MSPHM is constructed as follows. Because the potential outcomes $Y_{t,\overline{a}}$ of each subject are partly unobserved - instead only outcomes Y_t for the actual received exposures $\overline{a}$ are observed - the MSPHM cannot be constructed by only using the observed data. It is however possible to generate the distribution of the missing $Y_{t,\overline{a}}$, and this by upweighting each observation with actual $\overline{a}$ by the inverse probability of experiencing this specific $\overline{a}$. Hereby, it treats unobserved potential outcomes $Y_{t,\overline{a}}$ as missing observations from the distribution of potential outcomes, and will rely on upweighting according to the probability or propensity of having the observed data (ie. having actual exposure history $\overline{a}$) to create a population in which everybody experienced $\overline{a}$. If upweighting is repeated for all possible $\overline{a}$, we will thus create a pseudo-population of potential outcomes Y_t under all possible exposure regimes $\overline{a}$.

Upweighting by the inverse probability of experiencing exposure history $\overline{a} = (a_1, a_2)$ enables identifying the distribution of potential outcomes under the causal DAG of Figure (1.1) - without C - as follows. We start with the average of the outcome Y_2 that is weighted for the inverse probability of exposure for subjects

with $I(a_1, a_2) = 1$, or those having $\overline{a} = (a_1, a_2)$:

$$\begin{aligned}
& E\left\{\frac{I(A_1 = a_1, A_2 = a_2)}{f(A_2 = a_2|L_2, A_1, L_1)f(A_1 = a_1|L_1)}Y_2\right\} \\
= \; & E\left\{\frac{I(A_1 = a_1, A_2 = a_2)}{f(A_2 = a_2|L_2, A_1, L_1)f(A_1 = a_1|L_1)}Y_{2,(a_1,a_2)}\right\} \\
= \; & E\left[E\left\{\frac{I(A_2 = a_2)I(A_1 = a_1)}{f(A_2 = a_2|L_2, A_1, L_1)f(A_1 = a_1|L_1)}Y_{2,(a_1,a_2)}\middle| A_1, \overline{L}_2\right\}\right] \\
= \; & E\left[\frac{P(A_2 = a_2|L_2, A_1, L_1)I(A_1 = a_1)}{f(A_2 = a_2|L_2, A_1, L_1)f(A_1 = a_1|L_1)}E\{Y_{2,(a_1,a_2)}|A_1, \overline{L}_2\}\right] \\
= \; & E\left[\frac{I(A_1 = a_1)}{f(A_1 = a_1|L_1)}E\{Y_{2,(a_1,a_2)}|A_1, \overline{L}_2\}\right] \\
= \; & E\left[E\left\{\frac{I(A_1 = a_1)}{f(A_1 = a_1|L_1)}Y_{2,(a_1,a_2)}\middle| L_1\right\}\right] \\
= \; & E\left[\frac{P(A_1 = a_1|L_1)}{f(A_1 = a_1|L_1)}E\{Y_{2,(a_1,a_2)}|L_1\}\right] \\
= \; & E\left[E\{Y_{2,(a_1,a_2)}|L_1\}\right] \\
= \; & E\{Y_{2,(a_1,a_2)}\} \qquad (1.39)
\end{aligned}$$

where the first equality is due to consistency of exposure regime (1.8), the second, fifth and last to conditional expectation, and the third and sixth to SRA (1.9) at times $s = 2$ and $s = 1$ respectively. The weighted outcome is only defined under positivity assumption (1.10).

The weighting procedure shows that the parameters of a MSPHM can be estimated by *Inverse probability of exposure (IPE)* weighting. This is indeed how IPE-weighted estimation under a MSPHM adjusts for confounding of the association between exposure and outcome by time-dependent variables, not by including these variables in the functional part of the regression model (as in stratified models), but by using them to estimate the probability of exposure at each time and subsequently weighting observations by the inverse of these probabilities in an unadjusted analysis of the association between exposure and outcome. The weights can be interpreted as the number of copies of each observation that are necessary to form a pseudo-population in which there is no time-dependent confounding, but in which the causal effect of exposure on outcome is the same.

Similarly, one can further adjust the IPE-weighted estimator under the MSPHM for bias due to informative censoring by calculating supplementary weights derived from regression models that predict censoring based on time-varying subject characteristics. As before, this *Inverse probability of censoring (IPC)* weighting will create a pseudo-population in which A, L and C are unassociated. Because of this, the pseudo-population reflects the hypothetical situation in which all subjects would remain under follow-up until the last observation time, reflecting a situation without drop-out. IPC-weighting is only valid under ICA (1.12).

In practice, a MSPHM is fitted by using a pooled logistic regression model for the effect of exposure on the discrete-time hazard of outcome at t

$$P(Y_t|Y_{t-1}=0,\overline{a}_t,L_0;\beta^{\text{msm}}) \quad = \quad \text{expit}\{\gamma_{\text{msm}}(\overline{a}_t,L_0;\beta^{\text{msm}})\} \tag{1.40}$$

Model (1.40) is fitted to data that is inversely weighted at each t for the combined stabilised conditional probabilities of having observed exposure status and being uncensored until t, expressed as follows:

$$W_t^{\text{msm}} = W_t^{a,\text{msm}} \times W_t^{c,\text{msm}} \tag{1.41}$$

with

$$W_t^{a,\text{msm}} \quad = \quad \prod_{s=1}^{t} \frac{\pi_s^a(\overline{L}_s)}{\pi_s^a(L_0)} \tag{1.42}$$

$$W_t^{c,\text{msm}} \quad = \quad \prod_{s=1}^{t} \frac{\pi_s^c(\overline{A}_s,\overline{L}_s)}{\pi_s^c(A_s,L_0)} \tag{1.43}$$

$$\pi_s^a(.) \quad = \quad P(A_s=a_s|A_{s-1}=C_{s-1}=0,.) \tag{1.44}$$

$$\pi_s^c(.) \quad = \quad P(C_s=0|C_{s-1}=0,.) \tag{1.45}$$

Probabilities (1.44,1.45) are estimated from separately constructed pooled logistic regression models models for the discrete-time hazard of respectively $A_t=a_t$ and $C_t=0$. To prevent extreme weights, inverse conditional probabilities for individual patient days are stabilised with probabilities $\pi_s^a(L_0)$ and $\pi_s^c(A_s,L_0)$, derived from pooled logistic regression models similar to the ones above, but differing in

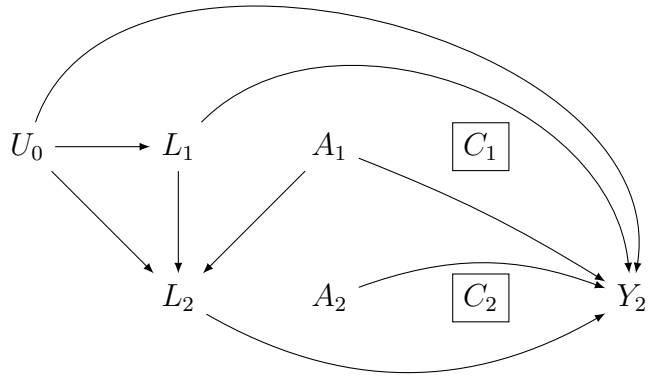


Figure 1.7: Causal directed acyclic graph depicting association between A_1 and Y_2 and between A_2 and Y_2 after Inverse probability of exposure and Inverse probability of censoring weighting.

that these adjust for baseline confounders L_0. The stabilisation is such that the weights W_t will be equal to 1 when L_t is unassociated with A in the data (Yu and van der Laan, 2006). When probabilities for exposure and for censoring need to be estimated from observed data, estimation under a MSPHM will be only valid if these models are correctly specified.

Calculation of MSPHM (1.40) is done using the *Generalised estimating equations* (Liang and Zeger, 1986) technique with independent working correlation structure, whose approximate variance estimator using the sandwich formula yields confidence intervals for the causal parameters of model (1.37). These intervals will be conservative when they do not take into account estimation of the parameters of the models used for calculation of IPE- and IPC-weights (Robins and Hernàn, 2009). As explained earlier, model (1.40) on weighted data is equivalent to MSPHM (1.37) for the counterfactual hazard of $Y_{t,\overline{a}}$. A MSPHM for $Y_{t,\overline{a}}$ can be fitted using standard statistical routines, which represents a major advantage relative to other statistical estimation routines for counterfactual outcomes, and which has lead to widespread use and implementation of MSPHMs in the literature.

The situation once this combined IPE-IPC weighting is applied and this pseudo-population is created can be visualised in the causal diagram of Figure (1.1) as

follows: arrows into exposure and censoring variables A_2, A_1, C_2 and C_1 will be removed, as a result of which there is no further confounding of the $A - Y$ association through non-causal paths passing through L_2, L_1 and U_0, as in the adapted causal DAG of Figure (1.7). Because of this, there is no further need to adjust for L_1 and L_2 in the analysis. As such, i.e. by avoiding adjustment via stratification-based methods, we can avoid inducing non-causal associations between A and Y, which initially arose because of conditioning on L_2. The causal effects of interest as shown in Figure 1.2 can therefore be unbiasedly estimated.

The use of a MSPHM to estimate the counterfactual hazard for mortality suffers from the weakness that goes with the interpretation of hazards. As mentioned above, the discrete-time hazard for the outcome Y, $P(Y_t = 1|Y_{t-1} = 0)$, is defined as the time-dependent probability of Y at a time t conditional on not having experienced Y until $t - 1$. Such conditioning on being outcome-free until $t - 1$ will lead to non-causal association and additional selection bias of the exposure-outcome relation (Hernàn, 2010). The problem is visualised in Figure 1.8, which is derived from the causal DAG of Figure 1.7 and updated with the inclusion of Y_1, the outcome variable at $t = 1$, to only show the non-casual paths between A_1 and Y_2 through U_0. Note that the hazard's conditioning on the past ($Y_1 = 0$) is visualised through the square surrounding the variable. The causal DAG shows that even when cancelling all relevant non-causal paths between joint exposure (A_1, A_2) and Y_2, the remaining paths between exposure A_1 and unmeasured prognostic variables U_0 will be responsible for residual non-causal associations between A_1 and Y_2 through conditioning on collider Y_1 in this particular path. To avoid this difficulty in interpretation, one can use the fitted MSPHM to predict conditional counterfactual hazards for specific exposure regimes, and then use these to calculate the corresponding risk of counterfactual survival for these regimes, as shown earlier using expression (1.5). Estimating the mean difference of risk of survival with a corresponding 95% confidence interval could then proceed by a series of bootstrap samples. Estimation of lag effects could proceed by calculating risk differences at specific end-of follow-up times that correspond with the onset of exposure of the studied regime and with the lag time used by the MSPHM.

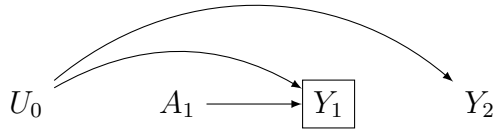


Figure 1.8: Causal directed acyclic graph depicting non-causal association between exposure A_1 and outcome Y_2 through intermediate outcome Y_1.

1.4.3 Structural nested accelerated failure time models

The *Accelerated failure time model* (Kalbfleisch and Prentice, 2002; Cox and Oakes, 1984) directly models the survival time T, in contrast to previously described proportional hazard models for the hazard rate. An Accelerated failure time model (AFTM) for a non-counterfactual outcome is of the form

$$T \stackrel{d}{=} T_b \times \exp(\psi' Z) \tag{1.46}$$

where $Z \equiv (L, A)$ is a vector of measured covariates, ψ a vector of parameters, and T_b the baseline survival time of subjects for which all covariates equal zero. The factor $\exp(\psi' Z)$ can be seen as an accelerating factor that contracts or expands baseline survival time T_b as a function of a subject's covariates Z. The "$\stackrel{d}{=}$" stands for equality in distribution, indicating that the equality holds for the respective distribution functions of the random variables (or functions thereof) in left and right parts of (1.46) .

A *Structural nested accelerated failure time model (SNFTM)* (Robins, 1992) adapts model (1.46) towards a counterfactual outcome and time-dependent exposure. A SNFTM for time-dependent exposure A_t is of the form

$$\begin{aligned} T_{t,0} \quad &\stackrel{d}{=} \quad (t-1) + \sum_{u=t}^{T} \exp\{\gamma_{\text{snm}}(\overline{A}_u, \overline{L}_u; \psi^0)\} \\ &\qquad \text{for } T \geq t \end{aligned} \tag{1.47}$$

with $T_{t,0}$ the counterfactual survival time corresponding to observed exposure history $\overline{A}_t$ until $t-1$ but set to zero exposure at t and thereafter, $\gamma_{\text{snm}}()$ a known function, and ψ^0 the unknown true parameter vector of dimension p that describes

the causal effect of exposure on log survival time scale. That this is an *accelerated failure time model* is obvious by virtue of it being derived from model (1.46). It is called *structural* because it models the counterfactual outcome $T_{t,0}$. See further why it is called a *nested* model. The parametrisation of the above SNFTM need not be restricted to the exposure A. It can be extended to any function of measured variables A and L as long as $\psi^0 \equiv 0$ and $a_t = 1$ implies $T_0 \stackrel{d}{=} T$ (with $T_{1,0} \equiv T_0$). The fact that interactions of exposure with time-dependent confounders L are allowed, represents a major advantage of SNFTMs over MSPHMs.

Going back to the example that motivated this study, we can use model (1.47) to verify what would happen with the distribution of survival times under a hypothetical intervention that would eliminate the onset of HAI. By mapping the distribution's observed survival time T into the counterfactual survival time T_0 under the absence of exposure, the SNFTM's ψ^0 parameter directly gives the causal effect of exposure on survival time. Because of this, the causal null hypothesis $H_0 : T \stackrel{d}{=} T_0$ corresponding to a zero effect of exposure on survival will correspond to testing $\psi^0 = 0$.

Consider SNFTM (1.46) with $\gamma_{\text{snm}}(\overline{A}_t, \overline{L}_t; \psi^0\} = \psi^0 A_t$ indexed by one-dimensional causal parameter ψ^0. For a subject with observed survival time $T = 2$ and being exposed at all times $t = 1, 2$ [giving exposure history $\overline{a} = (a_1, a_2) = (1, 1)$], observed survival times will be mapped into counterfactual survival times as follows:

$$\begin{aligned} T_{2,0} &= 1 + \exp(\psi^0 a_2) = 1 + \exp(\psi^0) \\ T_{1,0} &= \exp(\psi^0 a_1) + \exp(\psi^0 a_2) = 2\exp(\psi^0) \end{aligned} \tag{1.48}$$

When the objective is to measure the joint effect of time-varying exposure at t and $t-1$, we can postulate a SNFTM with $\gamma_{\text{snm}}(\overline{A}_t, \overline{L}_t; \psi^0\} = \psi_1^0(1 - A_{t-1})A_t + \psi_2^0 A_{t-1} A_t$ indexed by causal parameter vector $\psi^0 = (\psi_1^0, \psi_2^0)$. Continuing our example, the relevant part of the exposure history at $t = 2$ then becomes $(a_0, a_1, a_2) = (0, 1, 1)$. Counterfactual survival times will then become

$$\begin{aligned} T_{2,0} &= 1 + \exp\{\psi_1^0(1 - a_1)a_2 + \psi_2^0 a_1 a_2\} \\ &= 1 + \exp(\psi_2^0) \end{aligned} \tag{1.49}$$

$$\begin{aligned} T_{1,0} &= \exp\{\psi_1^0(1-a_0)a_1 + \psi_2^0 a_0 a_1\} \\ &\quad + \exp\{\psi_1^0(1-a_1)a_2 + \psi_2^0 a_1 a_2\} \\ &= \exp(\psi_1^0) + \exp(\psi_2^0) \end{aligned} \tag{1.50}$$

The above creation of counterfactual survival times under model (1.47) explains why it is *nested*; this is because the SNFTM creates counterfactual survival times recursively from $t = T_m$ to $t = 1$, and conditional on covariate and (possibly) confounder history $(\overline{A}_t, \overline{L}_t)$, which can be described as nested sets of variable history, the ones at t nested within those at $t-1$ etc.

Estimation of ψ^0 proceeds through G-estimation (Robins, 1992): from a grid of candidate ψ's that are plausible, those values are sought that, after calculating $T_{t,0}(\psi)$ through SNFTM (1.47), give zero association with the exposure in a pooled logistic regression model for the conditional effect of $T_{t,0}(\psi)$ on the discrete-time hazard of exposure

$$E(A_t|\overline{A}_{t-1} = \overline{Y}_{t-1} = \overline{0}_{t-1}, \overline{L}_t) = \text{expit}[\psi_L^{A'}\overline{L}_t + \psi_T^{A'} g_t\{T_{t,0}(\psi), \overline{L}_t\}] \tag{1.51}$$

in which $E(A_t|\overline{A}_{t-1}, \overline{L}_t)$ is the conditional discrete-time hazard of exposure, ψ^A an unknown parameter vector, and $g_t()$ a vector function of $T_{t,0}(\psi)$ with dimension equal to dim(ψ). By using SRA (1.9), we will search for ψ values that yield $\hat{\psi_T^A} = 0$ when fitting model (1.51), a procedure that will be equivalent to estimating ψ^0.

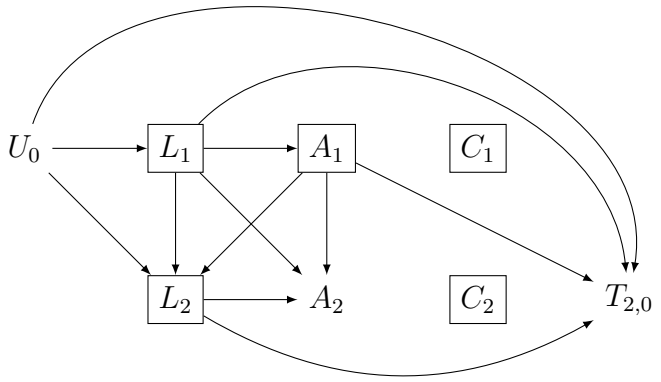
We demonstrate how the mapping of the counterfactual survival time $T_{t,0}(\psi)$ at $t = 1$ and $t = 2$ by means of G-estimation leads to unbiased estimates of the ψ^0. To do so, we again rely on causal diagrams. However, because a causal DAG assumes an underlying nonparametric model, which is in contrast with the use of a parametric SNFTM, the demonstration that follows is only informal. Figure 1.9 is derived from the causal DAG of Figure 1.1 but with Y replaced by T, and after adjusting for non-administrative censoring (visible by absence of arrows going into C_t at $t = 1, 2$). Eliminating exposure at $t = 2$ through SNFTM (1.47) leads to counterfactual survival time $T_{2,0}$, this will result in removal of outgoing arrow of A_2 into $T_{2,0}$ in causal diagram (a) of Figure 1.9. G-estimation will ensure that A_2 and $T_{2,0}$ are independent conditional on exposure and confounder history $(A_1, \overline{L}_t)$

at $t = 2$. Indeed, by conditioning on L_2, L_1 and A_1, visible in causal diagram (a) of Figure 1.9 through squares around these variables, all non-causal paths between A_2 and $T_{2,0}$ will be blocked. Counterfactual survival time $T_{1,0}$ will be created by further removing the effect of exposure at $t = 1$, G-Estimation now verifies conditional independence between $T_{1,0}$ and A_1 (given L_1), visible through blocked non-causal paths between these two variables in causal diagram (b) of Figure 1.9. Note that diagram (b) shows outgoing arrows of A_1 to allow for a null direct effect of A_1 on $T_{1,0}$ by balancing the paths $A_1 \to T_{1,0}$ and $A_1 \to L_2 \to T_{1,0}$

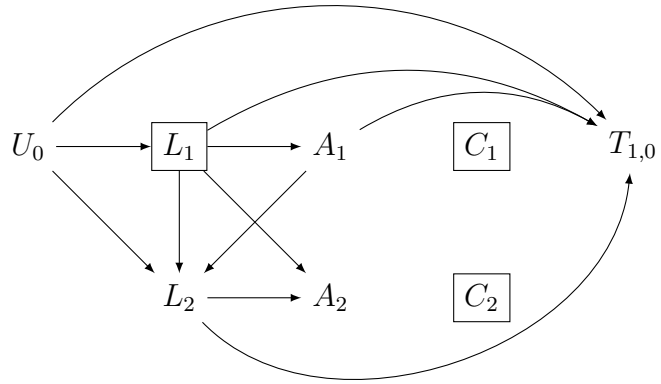
Since SNFTM (1.47) only relies on a selective group of subjects with observed or administratively censored survival time, we will explain in the next Section how the G-estimation procedure is adjusted for this. This includes G-estimation of ψ^0 under SNFTM (1.51) using an estimating function, and how this leads to approximate estimates of its asymptotic variance. Also, see Chapter 5 for details on how SNFTM (1.47) will be adapted to handle survival times T that are censored due to administrative end of follow-up.

1.4.4 Semiparametric efficiency

The previous sections introduced models along with estimation methods that deliver asymptotically unbiased estimates in the presence of measured time-dependent confounding of the exposure-outcome relationship. In this last section, we study asymptotically unbiased estimators which have minimal variance as well. What follows is for the sake of completeness and therefore only for the interested reader, because it will be only used to support particular derivations in the Appendices of Chapters 4 and 5. More specifically, we use results from semiparametric inference that allow us to find unbiased and efficient estimators for the causal parameters of MSPHMs and SNFTM. By applying these to SNFTM (1.47) for example, we tackle the problem that the default estimators under this model only use data from subjects with either observed survival time or whose outcome was not observed at the end of follow-up. We outline the most important results in the following paragraphs, see the monograph of Tsiatis (2006) and the master thesis of Vermeulen (2011) for in-depth explanations and proofs.



(a)



(b)

Figure 1.9: Causal directed acyclic graph depicting association between exposure A and survival time T in a G-estimation procedure under a Structural nested accelerated failure time model: non-causal paths between (a) exposure A_2 and counterfactual outcome $T_{2,0}$, and (b) exposure A_1 and counterfactual outcome $T_{1,0}$.

Regular and asymptotically linear semiparametric estimators

Assuming complete data (no missingness) for the time being, we consider our data (X, Y) [with $(U, A, L) = X$] as realisations of a semiparametric statistical model with joint density $p_{X,Y}(x, y; \psi, \eta)$, or

$$(X, Y) \quad \sim \quad p_{X,Y}(x, y; \psi, \eta) \tag{1.52}$$

where $p_{X,Y}(x, y; \psi, \eta)$ belongs to the class of densities $\mathcal{P}$ identified by the q-dimensional parameter of interest ψ and *nuisance parameter* η belonging to infinite-dimensional set H, as in

$$\mathcal{P} \quad = \quad \{p_{X,Y}(x, y; \psi, \eta) : \psi \in \Theta \subset \mathbb{R}^q, \eta \in H\} \tag{1.53}$$

In the above, nuisance refers to our understanding that the estimation of parameter η is merely a nuisance, ie. not the objective of the analysis.

For estimation of ψ, we will consider an *Asymptotically linear estimator (ALE)* $\hat{\psi}$ for the true parameter ψ^0; that is, an ALE estimator obeys

$$n^{1/2}(\hat{\psi} - \psi^0) = n^{-1/2} \sum_{i=1}^{n} IF^F(X_i, Y_i; \psi^0) + o_p(1) \tag{1.54}$$

with IF^F the q-dimensional *full-data influence function* of the estimator $\hat{\psi}$ for ψ^0, and having properties $E\{IF^F(X, Y; \psi^0)\} = 0^{q\times 1}$ and $E\{IF^F(X, Y; \psi^0) IF^{F'}(X, Y; \psi^0)\}$ being finite and nonsingular. The function $IF^F(X_i, Y_i)$ is referred to as the *i-th influence function* or the influence function of the i-th observation. Also, $o_p(1)$ is a stochastic variable that converges to zero in probability as n goes to infinity.

An ALE has a unique influence function IF^F and is *Consistent and asymptotically normal (CAN)*, as in

$$\hat{\psi} \quad \xrightarrow{p} \psi^0 \tag{1.55}$$

$$n^{1/2}(\hat{\psi} - \psi^0) \quad \xrightarrow{d} N\{0, E(IF^F IF^{F'})\} \tag{1.56}$$

with "$\xrightarrow{p}$" meaning convergence in probability, and "$\xrightarrow{d}$" convergence in distribution.

(1.55) implies that an ALE is asymptotically normal with asymptotic variance equal to the variance of its influence function. Finally, we impose suitable regularity conditions for $\hat{\psi}$ (Tsiatis et al., 2011)[Section 3.1], and therefore refer to these as a *Regular and asymptotically linear (RAL)* estimator.

M-estimators are an example of RAL estimators. These are characterised by $m(X, Y; \psi)$, a q-dimensional function of (X, Y) and ψ with properties $E\{m(X, Y; \psi^0)\} = 0^{q\times 1}$ and with finite and nonsingular second moments. The m-estimator $\hat{\psi}_n$ is then defined as the solution to $\sum_{i=1}^{n} m(X_i, Y_i; \psi) = 0$.

Geometry of full-data influence functions

The influence functions for ψ^0 can be presented as points (or vectors) in a Hilbert space of mean-zero q-dimensional functions $\mathcal{H}_q$. This is an infinite-dimensional abstract geometric function space, with the properties of having an inner product and norm defined as follows

$$< h_1, h_2 > \;=\; E(h_1' h_2) \tag{1.57}$$

$$||h|| \;=\; < h, h >^{1/2} \tag{1.58}$$

with $h_1, h_2, h \in \mathcal{H}_q$. From the definition, the inner product corresponds to the covariance of functions h_1 and h_2, therefore also called *covariance inner product*. Orthogonality between two influence functions ($h_1 \perp h_2$) is defined as $< h_1, h_2 >= 0$. The norm $||h||$ allows to define distance from the origin of the vectors in $\mathcal{H}_q$, and corresponds to the variance of influence function h. By defining covariance and variance in terms of geometric properties of $\mathcal{H}_q$, our objective will be to find and evaluate RAL estimators for ψ^0 with minimal variance. This will be done by constructing the influence function for our estimator that corresponds to the point closest to the origin of $\mathcal{H}_q$, hereby relying on the correspondence between norm (distance) and variance.

Letting $\theta = (\psi, \eta)$, and considering for the moment a finite r-dimensional nuisance parameter η, with $p = q + r$, define the *score vector* for $(X, Y) \sim$

$p_{X,Y}(x, y; \theta)$ as

$$S_\theta(X, Y; \theta^0) = \left. \frac{\partial \log p_{X,Y}(x, y; \theta)}{\partial \theta} \right|_{\theta=\theta^0} \tag{1.59}$$

or the p-dimensional vector of partial derivatives of the log-density with respect to θ and evaluated at the true parameter value θ^0. The finite-dimensional subspace of $\mathcal{H}_q$ spanned by score vector $S_\theta(X, Y; \theta_0)$ is called the *tangent space* $\mathcal{J}$:

$$\mathcal{J} = \{B^{q\times p} S_\theta(X, Y; \theta^0) : B^{q\times p} \in \mathbb{R}^{q\times p}\} \tag{1.60}$$

S_θ factorises into $\{S'_\psi(X, Y; \theta_0), S'_\eta(X, Y; \theta_0)\}'$ with S_ψ the q-dimensional vector of partial derivatives of the log-density with respect to parameter of interest ψ and S_η the r-dimensional vector of partial derivatives of the log-density with respect to nuisance parameter η. Define the *parametric nuisance tangent space* Λ as the finite-dimensional subspace of $\mathcal{H}_q$ spanned by S_η:

$$\Lambda = \{B^{q\times r} S_\eta(X, Y; \theta^0) : B^{q\times r} \in \mathbb{R}^{q\times r}\} \tag{1.61}$$

and $\mathcal{J} = \mathcal{J}_\psi \oplus \Lambda$, with $\mathcal{J}_\psi$ the tangent space of the parameter of interest ψ and $M \oplus N$ indicating the direct sum of subspaces $M, N \subset \mathcal{H}_q$.

Now returning to the case of an infinite-dimensional parameter η, the *semiparametric nuisance tangent space* Λ becomes the mean-square closure of all nuisance tangent spaces $\Lambda_\gamma = \{B^{q\times r} S_\gamma(X, Y; \psi^0, \gamma^0) : B^{q\times r} \in \mathbb{R}^{q\times r}\}$ of all parametric submodels $\mathcal{P}_{\psi,\gamma} \subset \mathcal{P}$, with $\mathcal{P}$ the class of densities defined by (1.52) and $S_\gamma(X, Y; \psi^0, \gamma^0)$ the score vector for the finite r-dimensional nuisance parameter γ of a parametric submodel $\mathcal{P}_{\psi,\gamma}$. That is, $\Lambda \subset \mathcal{H}_q$ is the space of all q-dimensional functions $h(X, Y) \in \mathcal{H}_q$ for which there exists a sequence $\{B_j S_{\gamma_j}(X, Y)\}_{j=1}^{+\infty}$ such that

$$||h(X) - B_j S_{\gamma_j}(X, Y)||^2 \to 0 \text{ as } j \to \infty \tag{1.62}$$

for a sequence of parametric submodels $\mathcal{P}_{\psi,\gamma_j}$ and $B_j \in \mathbb{R}^{q\times r_j}$ when $\gamma_j \in \mathbb{R}^{r_j}$.

Defining the semiparametric nuisance tangent space as above will be essential

in finding the *efficient influence function.* It can be shown that an influence function IF^F of a semiparametric RAL estimator $\hat{\psi}$ has the following properties:

$$E\{IF^F(X,Y)S'_\psi(X,Y;\psi^0,\eta^0)\} = I^{q\times q} \tag{1.63}$$

$$\Pi\{IF^F(X,Y)|\Lambda\} = 0, \text{ or } IF^F \perp \Lambda \tag{1.64}$$

with $\Pi[IF^F(X,Y)|\Lambda]$ the orthogonal projection of the influence function vector IF^F onto the nuisance tangent space Λ. The efficient influence function is then found by considering the *semiparametric efficient score* $S_{\psi,\text{eff}}(X,Y;\psi^0,\eta^0)$ in (1.63), given by

$$S_{\psi,\text{eff}}(X,Y;\psi^0,\eta^0) = S_\psi(X,Y;\psi^0,\eta^0) - \Pi[S_\psi(X,Y;\psi^0,\eta^0)|\Lambda] \tag{1.65}$$

which, as shown in Figure 1.10, is the residual obtained by subtracting from the score vector $S_\psi(X,Y;\psi^0,\eta^0)$ its orthogonal projection onto the semiparametric nuisance tangent space $\Pi[S_\psi(X,Y;\psi^0,\eta^0)|\Lambda]$. This will deliver the *efficient full-data influence function* $IF^F_{\text{eff}}(X,Y;\psi^0,\eta^0)$, or the unique influence function within $\mathcal{J}_\psi \oplus \Lambda$ with closest distance to the nuisance tangent space Λ, given by

$$IF^F_{\text{eff}}(X,Y;\psi^0,\eta^0) = E(S_{\text{eff}}S'_{\text{eff}})^{-1}S_{\text{eff}}(X,Y;\psi^0,\eta^0) \tag{1.66}$$

Deriving an optimal estimator for the restricted moment model

We show how efficient full-data influence function (1.66) leads to an estimator for ψ. First, consider the *Restricted moment model (RMM)* defined by

$$E(Y|X) \;\; = \;\; \mu(X;\psi), \tag{1.67}$$

which models the conditional expectation of Y given X as a known function of X and p-dimensional parameter ψ. Function (1.67), which can be rewritten as $E\{Y-\mu(X,\psi)|X\} = 0$, formulates the sole restriction on the joint density of X and Y. In what follows, we will study RMMs with $\mu(X,\theta) = \text{expit}(\psi' X^*)$, $X^* = (1,X)'$ and binary Y, which then becomes a logistic regression model.

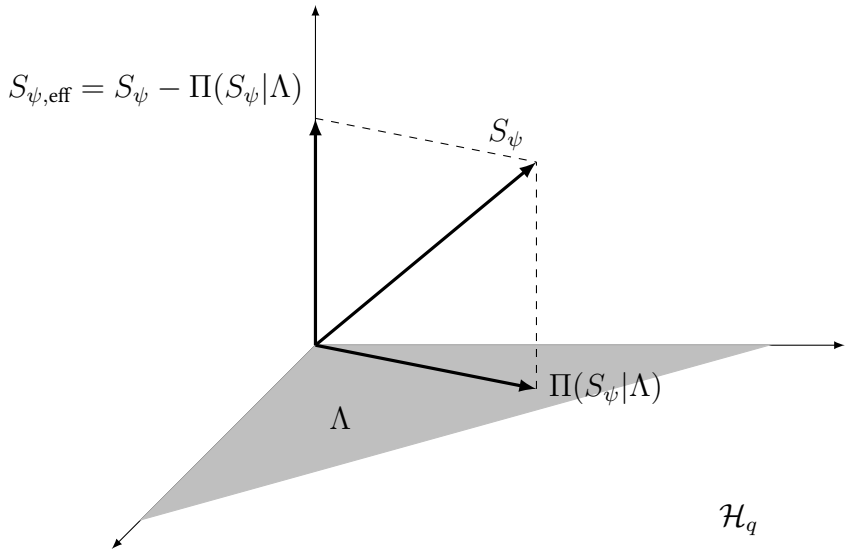


Figure 1.10: Orthogonal projection of the score vector S_ψ onto the semiparametric nuisance tangent space Λ and derivation of the semiparametric efficient score $S_{\psi,\text{eff}}$.

We consider joint densities for variables (Y, X) that can be written as

$$p_{YX}(y, x; \psi, \eta) \quad = \quad \eta_1\{y - \mu(x; \psi), X\}\eta_2(x), \tag{1.68}$$

with

$$\eta_1\{y - \mu(x; \psi), X\} \quad = \quad p_{Y-\mu|X}\{y - \mu(x; \psi)|x\} \tag{1.69}$$

$$\eta_2(x) \quad = \quad p_X(x) \tag{1.70}$$

or $\eta_1\{y - \mu(x; \psi), X\}$ the conditional density of $Y - \mu(X; \psi)$ given X with restriction $E(Y - \mu(X; \psi)|X) = 0$, and $\eta_2(x)$ the density of X. In the above, $\eta_1(.)$ and $\eta_2(.)$ can be viewed as infinite-dimensional nuisance parameters.

By deriving the semiparametric nuisance tangent space Λ, and then using criteria (1.63-1.63) for RAL full data influence functions for parameter ψ of RMM (1.67), the class of RAL influence functions is found to be (Tsiatis et al., 2011)[Section 4.5]

$$\left\{[E\{A(X)D(X)\}]^{-1}A(X)\{Y - \mu(X, \psi)\}\right\} \tag{1.71}$$

with $A(X)$ an arbitrary (non-trivial) p-dimensional function of X and $D(X) = \partial\mu(X,\psi)/\partial\psi$. This leads to RAL m-estimator $\hat{\psi}_n$ for ψ that solves estimating equation

$$\sum_{i=1}^{n} A(X_i)\{Y_i - \mu(X_i,\psi)\} \;=\; 0 \tag{1.72}$$

also known as *Generalised estimating equations (GEE)* (Liang and Zeger, 1986), with $\hat{\psi}_n$ a GEE-estimator. The efficient influence function is found by deriving the efficient score, which becomes

$$S_{\psi,\text{eff}}(Y,X) \;=\; D(X)'V(X)^{-1}\{Y - \mu(X,\psi)\} \tag{1.73}$$

with $V(X) = \text{var}(Y|X)$ the conditional variance of Y given X. The efficient influence function then becomes

$$IF^{F}_{\text{eff}}(Y,X) \;=\; [E\{D(X)'V(X)^{-1}D(X)\}]^{-1}D(X)'V(X)^{-1}\{Y - \mu(X,\psi)\} \tag{1.74}$$

yielding an optimal estimator $\hat{\psi}_n$ for ψ as the solution to estimating equation

$$\sum_{i=1}^{n} D(X_i)'V(X_i)^{-1}\{Y_i - \mu(X_i,\psi)\} \;=\; 0 \tag{1.75}$$

Applying the above to a logistic regression model, under which $D(X) = X^*V(X)$ and $V(X) = \mu(X,\psi)\{1-\mu(X,\psi)\}$, we obtain the optimal estimating equation

$$\sum_{i=1}^{n} X_i^*\{Y_i - \mu(X_i,\psi)\} \;=\; 0 \tag{1.76}$$

We now make the link to SNFTM (1.47) of Section 1.4.3. The G-estimation procedure of the causal parameter of the SNFTM assesses conditional independence under SRA (1.9) between $g_t\{T_{t,0}(\psi)\}$, the p-dimensional function of the

counterfactual survival time, and exposure A_t under the pooled conditional logistic regression model for the discrete-time hazard of exposure (1.51). We now consider function

$$U^{\text{T,F,snm}}(\psi) = \sum_{t=1}^{T} U_t^{\text{F,snm}}(\psi) \tag{1.77}$$

with

$$U_t^{\text{F,snm}}(\psi) = g_t\{T_{t,0}(\psi)\}\{A_t - E(A_t|\overline{A}_{t-1}, \overline{L}_t; \psi^A)\} \tag{1.78}$$

The above function $U^{\text{T,F,snm}}(\psi)$, with dimension equal to that of ψ, is the part within the summation of estimating equation (1.76), but applied to estimation of parameter ψ_T^A of the $g_t\{T_{t,0}(\psi)\}$ vector in pooled logistic regression model (1.51) for the conditional discrete-time hazard of exposure. Under SRA (1.9), the hypothesis $\psi = \psi^0$ will correspond to $\psi_T^A = 0$ in (1.51). The estimating equation

$$U^{\text{F,snm}}(\psi) = \sum_{i=1}^{n} U_i^{\text{T,F,snm}}(\psi) = 0. \tag{1.79}$$

will then deliver an asymptotically unbiased estimator $\hat{\psi}$ of causal effect parameter ψ^0. The function $U^{\text{F,snm}}(\psi) = 0$ can be viewed as an unstandardised score statistic for the null hypothesis $\eta = 0$ in model (1.51). Because $n^{-1/2}U(\psi)$ is asymptotically normally distributed with mean zero and variance given by $\Sigma\{U_i^{T,F,snm}(\psi)\}$, the variance-covariance matrix of $U_i^{T,F,snm}(\psi)$, optimisation of $U^{T,snm}(\psi)$ is usually done by calculating the test statistic

$$S = n^{-1}U^{F,snm}(\psi)'\Sigma\{U_i^{T,F,snm}(\psi)\}^{-1}U^{F,snm}(\psi) \tag{1.80}$$

The point estimate $\hat{\psi}_n$ of ψ^0 is the value of ψ that gives $S = 0$. The score statistic can be also used to obtain 95% confidence bounds for $\hat{\psi}_n$, by finding values around $\hat{\psi}_n$ that give $S(\psi) = \chi^2_{0.95}(p)$, or the Chi-square statistic corresponding with cumulative probability of 0.95 and p degrees of freedom. Alternatively, consider following Taylor expansion of $U(\hat{\psi}_n) \equiv U^{F,snm}(\hat{\psi}_n)$ around ψ^0:

$$0 = n^{-1/2}U(\hat{\psi}_n) = n^{-1/2}U(\psi^0) + n^{-1}\frac{\partial U(\psi^0)}{\partial \psi}n^{1/2}(\hat{\psi} - \psi^0) + o_p(1) \tag{1.81}$$

which leads to the following version of equation (1.54) showing asymptotic linearity of $\hat{\psi}$:

$$n^{1/2}(\hat{\psi}_n - \psi^0) = -n^{1/2} \left\{ \frac{\partial U(\psi^0)}{\partial \psi} \right\}^{-1} U(\psi^0) + o_p(1); \tag{1.82}$$

and the following approximation for the asymptotic variance of $\hat{\psi}$:

$$\Sigma(\hat{\psi}_n) = n \left\{ \frac{\partial U(\hat{\psi}_n)}{\partial \psi} \right\}^{-1'} \hat{\Sigma}\{U_i(\hat{\psi}_n)\} \left\{ \frac{\partial U(\hat{\psi}_n)}{\partial \psi} \right\}^{-1} \tag{1.83}$$

also called the sandwich variance (Robins, 1992; Tsiatis, 2006). In the above, we assumed for the sake of exercise that the nuisance parameter ψ^A of the exposure model (1.51) is known, ie. does not need to be estimated. We explain in Chapter 5 how we account for estimation of this parameter.

Geometry of observed-data influence functions

When data are subject to missingness, the objective of the analysis becomes to estimate the causal effect parameter ψ^0 in the scenario where no missing data would occur. As mentioned above, the full data (C, X, Y) contains the missingness variable C that has value 1 when variable Y for this observation is missing and 0 otherwise. The density of the full data becomes

$$P_{C,X,Y}(c, x, y; \phi, \psi, \eta) = P(C = c|X, Y; \phi) P_{X,Y}(x, y; \psi, \eta) \tag{1.84}$$

with $P(C = c|X, Y; \phi)$ the density of the missingness mechanism identified by parameter vector ϕ.

The observed data is $\{C, X, (1 - C)Y\}$. To generalise the notation for the missingness mechanism in the presence of longitudinal data, we define the new variable $\mathcal{C}$ that either denotes the time-point t at which censoring of outcome variable Y occurs, or has value ∞ in case the outcome event $Y = 1$ is observed. We then describe the observed data as combinations of variable $\mathcal{C}$ and $G_{\mathcal{C}}(x, y)$, the function (with realised value g_c) that maps the full data into the observed data,

or

$$\{\mathcal{C}_i, G_{\mathcal{C}_i}(X_i, Y_i)\}\ i = 1, .., n \tag{1.85}$$

which will give $P(\mathcal{C}|X, Y) = P(\mathcal{C}|X)$ under ICA (1.12) and will lead to vectors $\{\infty, (X, Y)\}$ and $\{t, (X)\}$ with $t = 1, .., T_m$. The observed data density can now be obtained by

$$\begin{aligned} P_{\mathcal{C},G_{\mathcal{C}}(X,Y)}(c, g_c; \phi, \psi, \eta) &= \int_{y:G_c(x,y)=g_c} P(\mathcal{C} = c|x, y; \phi) P_{X,Y}(x, y; \psi, \eta) dy \\ &= \int_{y:G_c(x,y)=g_c} P(\mathcal{C} = c|x; \phi) P_{X,Y}(x, y; \psi, \eta) dy \\ &= P(\mathcal{C} = c|x; \phi) \int_{y:G_c(x,y)=g_c} P_{X,Y}(x, y; \psi, \eta) dy \end{aligned} \tag{1.86}$$

Note that the model for the missingness mechanism $P(\mathcal{C} = c|X = x; \phi)$ does not depend on the data that gets mapped to being missing, and therefore can be placed outside of the integral. Due to this, the log-density of the observed data gets decomposed into

$$\log P(\mathcal{C} = c|X = x; \phi) + \log \int_{y:G_c(x,y)=g_c} P_{X,Y}(x, y; \psi, \eta) dy \tag{1.87}$$

which implies that with missing data, the observed-data nuisance tangent space spanned by the score vectors of the two nuisance parameters ϕ and η can be decomposed into the direct sum $\Lambda = \Lambda_\phi \oplus \Lambda_\eta$, with Λ_ϕ and Λ_η the semiparametric nuisance tangent spaces for parameters ϕ and η respectively, and with $\Lambda_\phi \perp \Lambda_\eta$; see Tsiatis et al. (2011)[Section 8.3] for proof.

When considering the geometry of full-data influence functions $IF^F(X, Y; \psi^0, \eta^0)$ for parameter ψ^0 and deriving $\Lambda_\eta^\perp$, the orthogonal complement of the nuisance tangent space for parameter η, we arrive at observed-data influence functions IF^{obs} of the form

$$\frac{I(\mathcal{C} = \infty)}{P(\mathcal{C} = \infty|X, Y; \phi)} IF^F(X, Y, \psi^0, \eta^0) + L_2\{\mathcal{C}, G_{\mathcal{C}}(X, Y)\} \tag{1.88}$$

with

$$E_\phi[L_2\{\mathcal{C}, G_\mathcal{C}(X,Y)\}|X,Y] = 0 \tag{1.89}$$

The first part of influence function IF^{obs} differs from a typical full-data influence function IF^{F} in that it only takes into account complete cases (having $\mathcal{C} = \infty$), which are inversely weighted by $P(\mathcal{C} = \infty|X, Y; \phi)$, their conditional probability of being observed. The second part of IF^{obs} is $L_2\{\mathcal{C}, G_\mathcal{C}(X,Y)\}$, an arbitrary $q-$dimensional function with specific properties of using observed data (therefore from complete as well as censored cases), and having mean zero under the full data distribution and the true model for censoring. Because the function L_2 augments the first part of influence function IF^{obs} with data from censored cases, the space Λ_2 of all functions L_2 is called the "augmentation space". Following from these arguments, an estimator that is derived from influence function IF^{obs} with function L_2 set to zero will be called an *Inverse probability of censoring weighted (IPCW) estimator*, while an estimator using the two parts of IF^{obs} will be called an *Augmented Inverse probability of censoring weighted (A-IPCW) estimator*.

Further projecting influence function IF^{obs} (1.88) onto $\Lambda_\phi^\perp$, the orthogonal complement of the nuisance tangent space for parameter ϕ, as in

$$\begin{aligned} &\left\{\frac{I(\mathcal{C}=\infty)}{P(\mathcal{C}=\infty|X,Y;\phi)}IF^F + L_2\right\} \\ -\quad &\Pi\left\{\frac{I(\mathcal{C}=\infty)}{P(\mathcal{C}=\infty|X,Y;\phi)}IF^F + L_2\middle|\Lambda_\phi\right\} \end{aligned} \tag{1.90}$$

and using that $\Lambda_\phi \subset \Lambda_2$, we obtain [see Theorem 10.1 of (Tsiatis, 2006) for details]

$$\left\{\frac{I(\mathcal{C}=\infty)}{P(\mathcal{C}=\infty|X,Y;\phi)}IF^F\right\} - \Pi\left\{\frac{I(\mathcal{C}=\infty)}{P(\mathcal{C}=\infty|X,Y;\phi)}IF^F\middle|\Lambda_2\right\} \tag{1.91}$$

which is the orthogonal complement of the first part of complete-case influence function (1.88) after projecting it onto augmentation space Λ_2. Estimators derived from influence function (1.91) have been shown to be *optimal* within the class of semiparametric RAL observed-data estimators (1.88) under the model defined by the restrictions of the joint density $p_{X,Y}(x, y; \psi, \eta)$ and censoring model $P(\mathcal{C}|X =$

$x;\phi)$, where "optimal" refers to the corresponding estimator having smallest asymptotic variance.

An IPCW G-estimator for the structural nested accelerated failure time model

In the previous section, we created an estimator for the causal parameter ψ^0 of a SNFTM when no missingness of the outcome variable Y occurs. In the presence of censoring of Y, we use the form of observed-data influence function (1.88) with function L_2 set to zero to create estimating function

$$U^{\text{T,obs,snm}}(\psi) = \sum_{t=1}^{T} \frac{I(C_T = 0)}{W_t^{c,\text{snm}}} U_t^{\text{F,snm}}(\psi) \tag{1.92}$$

with

$$W_t^{c,\text{snm}} = \prod_{s=t}^{T} \pi_s^c(\overline{L}, \overline{A}; \phi) \tag{1.93}$$

and

$$\pi_s^c(\overline{L}, \overline{A}; \phi) = P(C_t = 0 | \overline{C}_{t-1} = 0, \overline{A}_t, \overline{L}_t; \phi) \tag{1.94}$$

in which $U_t^{\text{F,snm}}(\psi)$ is the full-data estimating function for causal parameters under a SNFTM as defined in (1.78), $C_T = 0$ and $C_t = 0$ indicates subjects being uncensored at times T and t respectively, $\pi_s^c(\overline{L}, \overline{A}; \phi)$ is the conditional probability of being uncensored at time t, and $W_t^{c,\text{snm}}$ the cumulative conditional probability of remaining uncensored for the remainder of the subject's survival time T. The solution to estimating equation $U^{\text{obs,snm}} = \sum_{i=1}^{n} U_i^{\text{T,obs,snm}}(\psi) = 0$ will deliver an Inverse probability of censoring weighted (IPCW) G-estimator under a SNFTM indexing causal parameter ψ^0 .

Estimating equation (1.92) only uses data from complete cases and will be therefore inefficient. In Chapter 5 we will explore strategies on how to develop an Augmented Inverse probability of censoring weighted (A-IPCW) G-estimator

under a SNFTM that also uses data from censored cases.

An IPECW estimator for the marginal structural proportional hazards model

An estimator for the causal parameter β of a MSPHM as estimated by an Inverse probability of exposure and censoring weighted (IPECW) pooled logistic regression model for the discrete-time hazard of the outcome, can be constructed by taking as estimating function

$$\begin{aligned} U^{\text{T,msm}}(\beta) &= \sum_{t=1}^{T} \sum_{\overline{a}_t} \frac{I(\overline{A}_t = \overline{a}_t) I(C_t = 0)}{W_t^{\text{msm}}} \\ &\quad \times (\overline{a}_t, L_0)' \{ Y_t - P(Y_t | Y_{t-1} = C_{t-1} = 0, \overline{a}_t, L_0; \beta) \} \end{aligned} \tag{1.95}$$

and then solving

$$U^{\text{msm}}(\beta) = \sum_{i=1}^{n} U_i^{T,\text{msm}}(\beta) = 0 \tag{1.96}$$

for β. In (1.95), W_t^{msm} is, as defined earlier in (1.41), the cumulative multiplied conditional probabilities of the observed exposure regime $\overline{A} = \overline{a}$ and of remaining uncensored until time t.

From the above, we see that the results that lead to the derivation of semiparametric estimators for missing data can be used to construct estimators for average causal effects. This is done by considering the potential outcome under a particular exposure regime as an outcome that is subjected to missingness. The exposure variable then acts as an indicator of missingness, using that for each subject the observed value of exposure will mark the actually observed potential outcome. This way, the Ignorable censoring assumption (ICA) (1.12) and the Sequential randomisation assumption (SRA) (1.9) are actually analogues of a missing data estimation problem, the former for identification of outcomes that are unobserved due to censoring, the latter for identification of unobserved potential outcomes. The same analogy holds for the assumptions of Positivity of risk of remaining uncensored (1.13) and of exposure risk (1.10). This way, replacing the censoring by

the exposure indicator in equation (1.86) and using SRA will lead to an observed data likelihood that forms the basis for G-computation algorithm (1.33). Likewise, a similar weighted complete-case estimator as (1.88) can be developed by considering a mapping from observed data into full data function spaces, with the latter now denoting the space of influence functions based on potential outcomes. This is the basis for the *Inverse probability of exposure and censoring weighted (IPECW) estimator*, defined as the solution to estimating equation (1.96), and on which we relied in Section (1.4.2) to derive causal parameters under a MSPHM.

CHAPTER 2

Infections acquired in intensive care units: results of the national surveillance in Belgium, 1997-2010

This chapter is based on the following article: Mertens, K., Morales, I. and Catry, B. (2013) "Infections acquired in intensive care units: results of national surveillance in Belgium, 1997-2010," *Journal of Hospital Infection*, 84(2): 120-5.

Summary

This article provides the methodology and results from the Belgian surveillance for infections acquired in intensive care units (ICU) for the period 1997-2010. Since 1997, ICUs within acute care hospitals are encouraged by federal law to participate to national multicentric prospective observational surveillance. This allows acute care hospitals to follow locally their infection incidence and enable for comparison of incidence with national and European reference data. A protocol and software tool for data collection was developed, case definitions and methodology follows those from the European center for disease prevention and control. For 2010, 18 hospitals contributed data on 59 observation quarters, 6 478 ICU patients and 52 593

ICU patient days. The mean incidence for ICU-acquired pneumonia and intubation-associated pneumonia (IAP) was 13 per 1000 patient days and 12 per 1000 intubation days, respectively. The mean incidence for ICU-acquired, central vascular catheter-associated (CAB), and central vascular catheter-associated primary bloodstream infections (CAPB) were 3.2 per 1000 patient days, 2.6 per 1000 catheter days, and 3.2 per 1000 catheter days, respectively. During 1997-2010, stable trends of ICU-acquired pneumonia and bloodstream infections were observed, together with decreasing trends for IAP and CAB, and a stable trend for CAPB.

2.1 Introduction

The risk for acquiring Healthcare-associated infection (HAI) in Intensive care unit (ICU) is higher than in other hospitals wards, due to the patient's severe underlying health conditions and increased exposure to medical interventions and invasive devices (Gordts et al., 2010; Torres et al., 2009; Valles and Ferrer, 2009). The association of infection with morbidity and mortality in ICU is also substantially higher compared with other wards (Vrijens et al., 2012). Surveillance of HAI is defined as the continuous and systematic collection, analysis and interpretation of data on the occurrence of these infections, their risk factors and outcome parameters, and is widely acknowledged as a valuable component in a strategy for the prevention and control of this type of infection (Gastmeier et al., 2000a; Gaynes et al., 2001; Haley et al., 1985). This article aims to provide the methodology and output of the Belgian National surveillance of infections acquired in intensive care units (NSIH-ICU) for the period 1997-2010.

2.2 Materials & Methods

2.2.1 Legal context

The NSIH-ICU protocol was developed in 1997 by the "National surveillance of infections in hospitals (NSIH)" program of the Scientific institute of public health

(IPH) in close collaboration with the Belgian Society of Internal Medicine, and launched with a financial incentive to encourage participation. In 2004, the protocol was modified according to the Hospitals in Europe link for infection control through surveillance (HELICS) project (Suetens et al., 2007).

Since 2007, Belgian national surveillance of HAI is outlined in the law (Belgisch staatsblad, 2007) and includes, besides the surveillance of ICU-acquired infections, 7 other HAI surveillance protocols. The objective of national surveillance is (1) to provide the necessary standards, definitions and tools for the organisation of surveillance and the follow-up of results within the healthcare setting (local objective), and (2) to set-up a national database of surveillance data (national objective). This enables participating hospitals or wards to compare their results with those from the national population (benchmarking), and allows national stakeholders such as the Belgian antibiotic policy coordination committee (Goossens et al., 2008) to monitor national trends.

2.2.2 Data collection

Collection of surveillance data on the occurrence of HAI is performed prospectively and during a minimum observation period of 3 months. Followed infections are ICU-acquired pneumonia, Bloodstream infection (BSI), urinary tract infection and catheter-related infection. An infection is defined as ICU-acquired when occurring after day 2 within the unit. Infections occurring after discharge from the ICU are excluded, due to the time-consuming nature of organising such type of surveillance. Device-associated infections are defined as having a relevant invasive device in the two days preceding the onset of infection, with relevant device being endotracheal intubation for pneumonia and Central vascular catheter (CVC) for BSI. For BSI, the origin of the infection (unknown, catheter, secondary) is to be encoded as well, thus allowing calculating the number of primary BSI (catheter or unknown origin). Case definitions are those implemented in 2004 by the HELICS project as taken over in 2007 by the European center of disease prevention and control (ECDC).

Infection data is further completed by denominators which can be collected in two ways. In the light version of the protocol, aggregated denominators such as

the number of patients admitted and patient days are specified directly, whereas in the standard version they are calculated through data on each individual patient staying in the ICU for more than two days (for whom risk factors and outcome variables at admission, during hospital stay and at discharge, irrespective of developing an infection or not are recorded). All surveillance data entry is performed by means of the locally installed NSIHwin software, which is developed by the NSIH program itself, regularly updated, and freely available to participants.

2.2.3 Output variables & analysis

Both (light and standard) versions of the protocol allow the calculation of the cumulative incidence (number of newly infected patients over total patients) and the incidence density (number of new infections per 1000 patient days) for each infection type, as well as the incidence densities of intubation-associated pneumonia over intubation days, of Central vascular catheter-associated bloodstream infections (CAB) over CVC days, and of CVC-associated primary BSI per 1000 CVC days. The standard version of the protocol allows finer adjustment of infection incidence for the case-mix of the ICU population case-mix and the degree of invasive device use. Participating hospitals receive a confidential feedback report shortly after sending their data to the NSIH program.

The indicators in this paper that we present on the incidence of infection and on the mean patient length of stay and invasive device use, are aggregated nationally and annually by means of the annual pooled database mean.

2.2.4 Cohort analysis

In order to analyse the evolution of particular indicators within a stable group of hospitals, a cohort of hospitals that participated during at least half of all surveillance periods was established. A trend analysis was done on the database mean of each type of infection incidence density, and this from a logistic regression model for the linear (on the logarithmic scale) trend of the daily odds of infection on patient- or device day-discretised data, and having the year as a single ordinal

predictor. To correct for the variability of infection incidence across hospitals, separate models were fitted for the hospital mean, and using Generalised estimating equations (GEE) (Liang and Zeger, 1986). Similar trend analyses were carried out on the mean length of stay in the ICU using linear regression, and for the daily odds of invasive device use (intubation and CVC) using logistic regression. Each model's coefficient for the yearly trend was recalculated to represent the change for the whole period (1997-2010).

All data are analysed by means of the statistical software package STATA v10 (STATA, 2007).

2.3 Results

A Total of 18 acute care hospitals participated to the NSIH-ICU surveillance in 2010, referring to an observation period of 59 trimesters, 6 478 ICU-patients and 52 593 ICU-patient days, 12 792 intubation and 24 763 CVC days. Although participation has steadily decreased since 1998, the number of surveillance periods illustrates relative intense or continuous monitoring among participating units (Figure 2.1). Note that participation denotes the number of hospitals, with several hospitals participating with more than one ICU (data not shown).

Figure 2.2 shows the annual evolution of mean length of stay in the ICU (left), use of invasive intubation (middle) and use of CVC (right). The mean length of stay has seen a substantial increase over the years: from 6.5 days in 1997 to 8.1 days in 2010. A relative stable trend was seen for invasive intubation use, from 318 to 389 days per 1000 patient days between 1997 and 2010. For CVC use, a decreasing trend from 742 to 615 CVC days per 1000 patient days was seen between 1997 and 2001, and a steady increase afterwards until 751 CVC days per 1000 patient days in 2010.

In 2010, the mean cumulative incidence of ICU-acquired pneumonia was 8.5%, the mean incidence density was 13 per 1000 patient days and 12 intubation-associated pneumonia per 1000 intubation days. The longterm evolution for pneumonia incidence (Figure 2.3) suggests a stable trend for ICU-acquired pneumonia

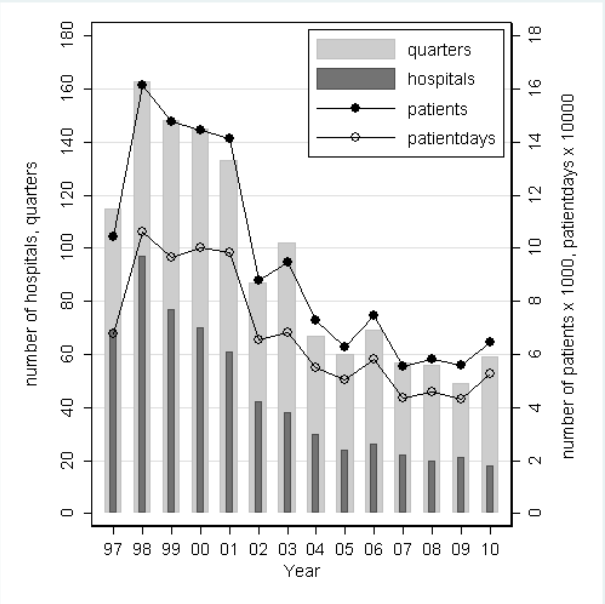


Figure 2.1: Evolution of participation and number of observed patients and patient days for the National surveillance of infections acquired in intensive care units (NSIH-ICU).

with incidences ranging between 7 and 15 per 1000 patient days. For intubation-associated pneumonia incidence, a substantial decrease was seen from 27 (in 1997) to 12 (in 2010) per 1000 intubation days.

The mean cumulative incidence of ICU-acquired BSI in 2010 was 2.5%, its mean incidence density was 3.2 per 1000 patient days, 2.6 CVC-associated BSI per 1000 CVC days, and 2.3 CVC-associated primary BSI per 1000 CVC days. Figure 2.4 shows a stable long term evolution of ICU-acquired BSI in the range of 2 to 4 per 1000 patient days. The evolution of the incidence of catheter-associated BSI suggests a decreasing trend from 4.7 (1997) to 2.6 (2010) per 1000 CVC days. A lesser decreasing trend was seen among CVC-associated primary BSI, from 3.0 (1997) to 2.3 (2010) per 1000 CVC days.

For both intubation-associated pneumonia and catheter-associated BSI, a low point in incidence (especially median) was reached directly after the introduction of the new HELICS case definitions in 2004. During a transient period, missing data were seen for the new variable ”invasive device use” upon which the definition of intubation- or catheter association was based (data not shown), and which could

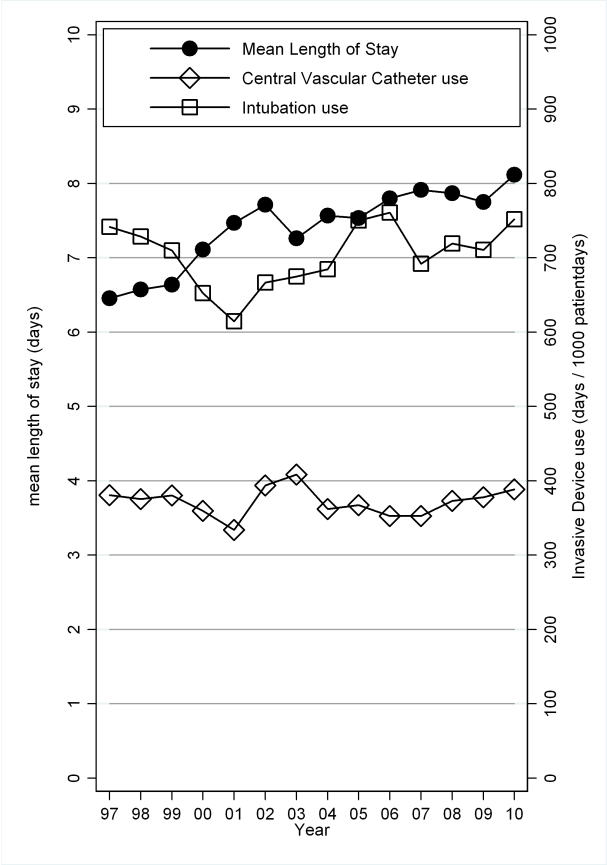


Figure 2.2: Evolution of mean length of stay, use of invasive intubation, and use of central vascular catheter (CVC) in intensive care units in Belgium, National surveillance of infections acquired in intensive care units (NSIH-ICU).

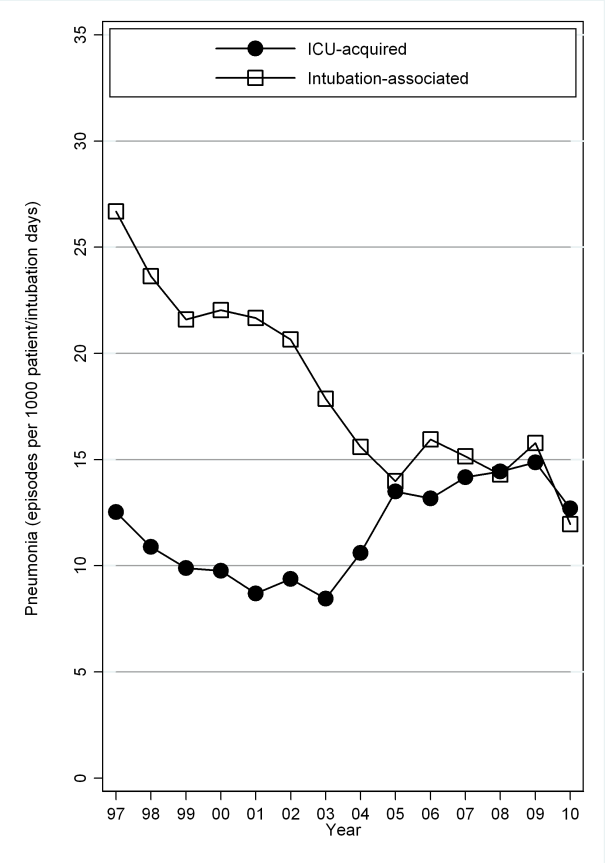


Figure 2.3: Evolution of incidence of intensive care unit acquired and invasive intubation-associated pneumonia in Belgium, National surveillance of infections acquired in intensive care units (NSIH-ICU).

explain this lowered incidence.

During 1997-2010, a total of 22 hospitals participated during at least 8 years. Their types were similar to the national distribution with 85% general, 10% teaching, and 5% university hospitals. This cohort contributed annually between 5 000 and 7 000 ICU admissions with at least 2 days of ICU stay and between 30 000 and 50 000 corresponding patient days in the ICU. On average, hospitals in this cohort contributed data for at least 3 surveillance periods per year of participation. Table 2.1 shows the results of the trend analysis. The mean length of stay shows a steady yearly increase, with a total increase of 1.8 days for the whole period. The use of invasive intubation in the cohort showed a 9% decrease in odds, while CVC

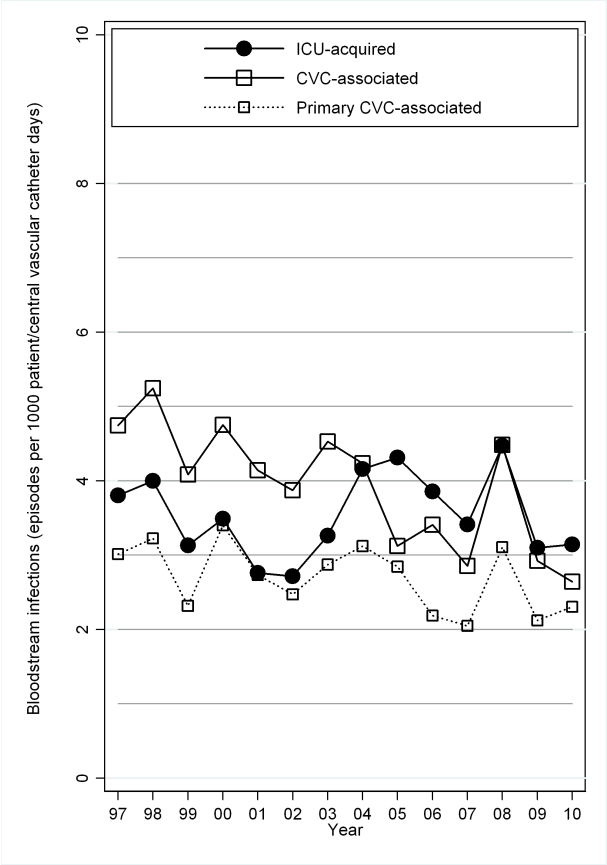


Figure 2.4: Evolution of incidence of intensive care unit acquired bloodstream infection, central vascular catheter associated bloodstream infection, and central vascular catheter associated primary bloodstream infection in Belgium, National surveillance of infections acquired in intensive care units (NSIH-ICU).

Indicator	Pooled mean Me/OR (95% CI)	Hospital mean Me/OR (95% CI)
Length of stay (mean days)	1.8 (1.7 to 1.9)***	1.8 (0.097 to 3.5)*
	invasive device use (daily odds)	
intubation	0.91 (0.89 to 0.93)***	0.92 (0.60 to 1.4)
CVC	1.2 (1.2 to 1.2)***	1.3 (0.52 to 3.0)
	pneumonia (daily odds)	
ICU-acquired	1.5 (1.4 to 1.7)***	1.5 (0.57 to 4.2)
intubation-associated	0.63 (0.55 to 0.71)***	0.63 (0.34 to 1.2)
	bloodstream infections (daily odds)	
ICU-acquired	1.2 (1.0 to 1.4)*	1.2 (0.67 to 2.1)
CVC-associated	0.78 (0.64 to 0.95)*	0.78 (0.47 to 1.3)
CVC-associated primary	1.1 (0.91 to 1.4)	1.1 (0.76 to 1.7)

Table 2.1: Trends of incidence of hospital-acquired infections, device-associated infections, mean length of stay and invasive device use in intensive care units in Belgium, 1997-2010; Me/OR = Mean increase for the whole period for length of stay in days, Odds for device use or infection ratio for all other indicators; 95% CI = 95% confidence interval and type I error level (p-value) of null hypothesis test of trend coefficient; ICU = Intensive care unit; intubation = endotracheal intubation; CVC = central vascular catheter; *p-value$<$.05, **p-value$<$.01, ***p-value$<$.001 represent significance level from Wald-test; Results derived from a cohort of 22 acute care hospitals that participated to the national surveillance of ICU-acquired infections in Belgium.

use showed a 20% increase in odds for the whole period. The evolution of mean infection rates of the cohort is largely in line with those of the total group of participants, with a 50% increase from 1997 to 2010 for ICU-acquired pneumonia and 30% increase for BSI, 37% decrease for intubation-associated pneumonia, 22% for CVC-associated BSI, and a stable trend for CVC-associated primary BSI (10% increase). These periodic trends were similar for the models for database mean and hospital mean. However, because the cohort had substantial variability of rates across hospitals, none of the periodic trends for the hospital mean (except mean length of ICU stay) achieved statistical significance.

2.4 Discussion

During the last 20 years many European countries have installed regional or national surveillance of ICU-acquired infections (Agodi et al., 2010; Carlet et al., 2009; Malacarne et al., 2008; van der Kooi et al., 2007; Zuschneid et al., 2007). Most of these networks use a standardised protocol that was derived or adapted from HELICS methodology, and because results are annually reported to ECDC, their epidemiological reports allow valid comparisons between networks as well as against a European reference. The incidence of pneumonia as estimated by the Belgian NSIH-ICU surveillance is higher than the overall European estimates for 2009 with 7.1% ICU patients with pneumonia, 7.8 ICU-acquired pneumonia per 1000 patient days and 14.5 intubation-associated pneumonia per 1000 intubation days (ECDC, 2011). Belgium has a relative low average length of ICU stay (in 2009: 7.8 days compared to 10.4 for Europe) as well as a low invasive intubation rate (37.4 per 100 patient days as compared to 54.9 for Europe).

The incidence of ICU-acquired pneumonia and BSI underwent a stable to light increasing trend in the period 1997-2010, but at the same time the mean length of stay of patients that were followed for this surveillance increased substantially. The incidence of both intubation-associated pneumonia and CVC-associated BSI, often the focus of targeted infection prevention programs (Bonten, 2011; Pronovost et al., 2006), showed a decreasing trend over the years. For pneumonia this is accompanied with a decrease in intubation use over the years, while for BSI an increased use of catheterisation is seen. The incidence of CVC-associated primary BSI - which excludes infections from secondary origin, and therefore focuses on the (most) preventable fraction - showed a decreasing trend in the overall group of participants, but this was not seen in the group of hospitals with most frequent participation.

While interpreting these results, the following points need to be taken into account. First, participation to the NSIH-ICU surveillance has decreased over the years, and undoubtedly, this might influence the interpretation of national incidences as data could have been contributed by a potentially selective subset of hospitals. One reason for this declining participation is the increased number of

hospital mergers which has lowered the number of eligible acute care hospitals over the years. To illustrate this, at the beginning of the national surveillance in 1997, 170 hospitals were eligible for participation, but this was reduced to 116 hospitals in 2011. Simultaneously, since 1997, other surveillances have been added to the list of national surveillances. Annual participation to the surveillances of Meticillin-resistant *Staphylococcus aureus* and *Clostridium difficile* became mandatory thereby prioritising these over other national programs such as the NSIH-ICU surveillance. Other factors such as the availability of local systems and pressure from consumer organisations to force public disclosure might also have resulted in lower participation. This limited but steady number of participants should be interpreted positively under the hypothesis that hospitals participating under the actual optional regime are more motivated as compared to earlier times when this surveillance was mandatory in certain regions of the country.

Second, the overall evolution of infection incidence among the overall group of hospitals was confirmed in the cohort of hospitals that participated during half of all surveillance periods. But, while such cohort analysis does not suffer from biases due to hospitals with infrequent participation and contributing extreme incidence, it remains driven by the limited number of hospitals that participated in recent years.

Third, relevant percentiles (25th, 50th, 75th) of the annual national distribution of hospital means for each indicator were not presented but showed substantial variation of annual rates between hospitals. This is confirmed by the trend analysis of the cohort data where none of the statistical significant trends of the pooled national means were confirmed by the analysis of hospital means. Such variation is also informative for the improvement that still can be achieved in the prevention of hospital-acquired infections in a multicentric context.

Hospitals participate in the underlying surveillance project based on its main objective: to decrease infection rates. However, looking at the trends presented in this article, this objective is only partly fulfilled. When trying to evaluate the added value of a national surveillance, the following points need to be made. First, the evidence surrounding the hypothesis that ”surveillance reduces infection rates” defines surveillance as the periodic monitoring accompanied by discussion

and interpretation of its results. The national surveillance project in itself only guarantees the first part of this process, because no information was collected on how participants used the collected data internally. Second, improved case-finding as well as variation in case mix might have influenced the observed trends. Third, evaluation of the long term impact of a national surveillance program should not only be based on the changed rates of its targeted infection types, but equally on the impact of these infections on mortality and morbidity outcomes. Fourth, analysing only the group of participating hospitals does not constitute a correct impact assessment because it lacks a proper control group. None of the mentioned points were the objective of this study.

In summary, acute care hospitals in Belgium are encouraged to participate to national surveillance. Its standardised tools allow following locally the incidence of ICU-acquired infections, and enable for comparison of hospital incidence with national and European reference data. For the entire period 1997-2010 and the total group of participants, we see stable trends for the incidence of ICU-acquired infection and decreasing trends for the incidence of device-associated infection.

CHAPTER 3

Marginal structural models to estimate the attributable effect of ICU-acquired infections on mortality

This chapter is based on an unpublished article written in collaboration with S. Vansteelandt, I. Morales and B. Catry.

Summary

The assessment of the attributable effect of Intensive care unit (ICU) acquired infection on mortality remains a controversial topic, this is partly assumed to be due to the choice of statistical methodology. Also, the effect of infection early versus late after its onset has never been estimated separately. We estimate these effects using methods from the field of causal inference. Unbiased effect estimation requires adjustment for baseline and time-varying risk factors of mortality and infection and additionally requires accommodating informative censoring of the survival time due to selective drop-out of patients. This is realised by fitting Marginal structural proportional hazards models. Data on 16 366 patients was derived from a national multicentric surveillance study (Belgium). Our analysis

yields adjusted hazard ratios of mortality of exposed versus unexposed patients equal to 1.1 [95% Confidence interval (CI) 0.8 to 1.5] for pneumonia and 1.5 (95% CI 0.9 to 2.6) for Bloodstream infection (BSI). Only the group of patients with intermediate severity at admission (Simplified acute respiratory score II 20-39) had increased attributable mortality for both pneumonia and BSI. The two types of infection differed in terms of the variation of their post-infection risk for mortality. For pneumonia, different attributable mortality was seen early (protective) versus late (harmful) after infection onset, a risk inversion that was not found for BSI.

3.1 Introduction

Despite the apparent negative effect on a patient's health status, the assessment of the attributable effect of Healthcare-associated infection (HAI) on mortality - i.e. the mortality risk due to the presence of infection - remains a controversial topic, with several studies describing estimates of the relative effect of infection on the risk of mortality ranging from being neutral to extremely risk increasing (Bercault and Boulain, 2001; Fagon et al., 1993; Girou et al., 1998; Heyland et al., 1999; Papazian et al., 1996; Timsit et al., 1996). One possible factor explaining this controversy is the failure to adjust (appropriately) for time-varying risk factors of infection, which are indicative of the subject's health status (such as severity scores) or the therapeutic activity that the subject did undergo during that period (Carlet, 2001; Carlet et al., 2001). Because patients who acquire infection generally have a poorer health condition than patients who do not, the analysis should adjust for time-varying risk factors associated with both infection-exposure and mortality to the extent possible, in order to achieve comparable groups of exposed and unexposed subjects. Failure to do so, for example by estimating a crude (unadjusted) effect or by merely adjusting for confounding variables collected at admission to the hospital, may yield biased effect estimates.

Adjustment for confounding commonly happens by stratification; that is, by including confounders as predictors in a regression model for the association between infection and mortality. In this article, confounding adjustment is instead

realised via weighted proportional hazards regression. Specifically, we will fit a Marginal structural proportional hazards model (MSPHM) (Hernàn et al., 2001; Robins and Hernàn, 2009), which belongs to a class of causal models for analysing the effect of time-varying exposures. This model will prevent two sources of bias that previous studies for the attributable effect of infection on mortality relying on stratification-based regression models suffer from and have thus far failed to acknowledge: time-dependent confounding and selective drop-out which can be explained by measured time-varying patient characteristics. Such standard stratification-based approaches which adjust for time-dependent confounders induce bias whenever, as is most likely the case in our setting, the considered confounders (for example daily use of mechanical ventilation) in the regression model are themselves affected by the exposure to infection. Technically, it can be shown that, by using such models, one can unbiasedly estimate the adjusted effect of the exposure at time t on the outcome at t, but not of the adjusted effect at previous times because adjustment for time-dependent confounders at t will distort the estimation of the exposure effect at previous times. This attributable lagged effect of infection on mortality has hardly been studied until now but is of particular interest as it gives further guidance on the clinical burden of infection (Muscedere et al., 2010). For example, it could provide insight in the result of anti-infectious treatment, as an outspoken harmful (beneficial) attributable effect of infection on risk for mortality in the first few days after onset could signify the failure (success) of a treatment.

Furthermore, standard proportional hazards regression approaches (which include baseline patient characteristics) also suffer from bias through selective dropout because they effectively assume that discharge from the hospital (i.e. censoring of the survival time), while possibly related to the baseline patient characteristics included in the substantive model of interest, is not further related to the actual survival time (Hernàn et al., 2004). This assumption of "Ignorable censoring conditional on baseline characteristics" is clearly violated because patients are discharged for reasons (prognostic factors) closely related to the endpoint under study (mortality). Because the patients who drop out thus represent a selective subset of the total group of patients in terms of prognostic factors arising before

the time of discharge, the analysis additionally needs to adjust for these variables.

3.2 Materials and methods

3.2.1 Study population and data collection

Follow-up data was obtained for a group of 46 Intensive care units (ICUs) that participated during a minimum three-month period to the National surveillance of infections acquired in intensive care units (NSIH-ICU) (Mertens et al., 2013) (Belgium) during the years 2002 and 2003. Besides data on occurring HAI, a participating ICU also needed to collect follow-up data for all patients admitted during the 3 month surveillance period. This includes intrinsic risk factors collected at baseline as well as data on daily exposure to invasive devices and antimicrobial treatment. HAIs were considered ICU-acquired if they occurred after the 2nd day of stay in the ICU. The target population for follow-up was therefore all patients with at least 3 ICU patient days. ICU follow-up was administratively censored to 30 days, meaning that patients who stayed longer than 30 days in the ICU, have a censored survival time of 30 days. Infected patients (cases) were those who suffered from one or more episodes of ICU-acquired pneumonia or Bloodstream infection (BSI) during their ICU stay. Case definitions for pneumonia and BSI followed those from the Hospitals in Europe link for infection control through surveillance (HELICS) European standard protocol (Suetens et al., 2007).

3.2.2 Statistical analysis

In this article, MSPHMs (Hernàn et al., 2001) are models for the marginal effect of an infection path (for example infection at day 5, or absence of infection throughout the stay in the hospital) on the counterfactual hazard for mortality under this infection path. The term ”Marginal” implies that the hazard for mortality is aggregated over all levels of measured time-dependent confounders. The counterfactual hazard for mortality under this infection path is defined as the mortality that

a subject would experience when being (hypothetically) exposed to a particular infection path, counterfactual to the one actually received. This model allows to contrast for the same population the counterfactual hazards under different infection paths (including the one under absence of infection), therefore its coefficients indexing infection-exposure have a causal interpretation. By using models for counterfactual outcomes, we assume that such outcomes are defined and have realistic interpretation (Hernàn, 2005). Formulating counterfactual outcomes is not new in the literature on this subject (Fagon et al., 1993; Bekaert et al., 2009, 2011; Bonten et al., 2004; Fagon et al., 1996; Rello and Valles, 1998; Vansteelandt et al., 2009), the rationale is that ICU-acquired infection is generally considered as a preventable adverse event, and, as such, we consider counterfactual outcomes to be generated under "the set of interventions that would prevent infection from taking place". Specifically, in the context of time-varying confounders, all variables considered to be part of such interventions should be left out of the adjustment process. The intrinsic baseline and extrinsic time-dependent covariates used to adjust the infection-mortality association are listed in Table 3.1.

Our MSPHM is essentially a proportional hazards model for mortality involving time-dependent infection status and baseline covariates, but no further time-varying covariates. In the model fitting process, each patient day is upweighted according to combined Inverse probability of exposure (IPE) and Inverse probability of censoring (IPC) probabilities until that day. Exposure is here defined as exposure to HAI, and censoring as discharge alive from ICU. This weighting procedure estimates the counterfactual outcomes mentioned above (Robins and Hernàn, 2009; Hernàn and Robins, 2006), it therefore overcomes the need to adjust via stratification and hence yields estimates that are not prone to the mentioned biases of standard regression methods. Exposure weights are applied to adjust for time-dependent confounders of the infection-mortality association, censoring weights were used to adjust for selective drop-out of patients being discharged alive before the administrative censoring date of 30 days. The procedure for the construction of weights is described in Appendix 3.5.1; this involves uni- and multivariate analysis to identify risk factors for onset of infection and censoring, as well as using these models to predict daily risks of infection and censoring and

Baseline indicator variables	gender, multiple trauma, acute coronary care
Baseline category variables	age (categories $<$40, 40-59, 60-69, 70-74, $\geq$ 80), SAPS II score* (categories $<$20 / 20-39 / 40-59 / $\geq$ 60), infection at admission (categories none / lower respiratory tract infection / bacteraemia / other / multiple infection), type of admission (categories medical / scheduled surgery / unscheduled surgery), antibiotic utilisation in 48 before or after admission (categories none / prophylactic antibiotic / therapeutic antibiotics / combination), prior surgery (categories no surgery / elective surgery / urgent surgery)
Time-varying indicator variables	mechanical ventilation, central vascular catheter, presence of a naso or oro-intestinal tube, feeding through a naso or oro-intestinal tube, parenteral feeding, stoma feeding, antibiotic therapy, antibiotic profylaxis, oral intubation, nasal intubation, tracheotomy intubation, surgery

Table 3.1: Baseline and time-varying covariates used to adjust the attributable effect of ICU-acquired pneumonia and bloodstream infection on mortality, using data from the National surveillance Of ICU-acquired infections, Belgium, 2002-2003; *SAPS = Simplified acute physiology score; ICU=Intensive care unit.

subsequent construction of weights.

MSPHMs for the effect of infection on mortality were fitted separately for pneumonia and BSI. Four models were fitted for each type of infection, the first indexed the effect as one parameter, the second stratified this effect for categories of Simplified acute physiology score II (SAPSII) score (Le Gall et al., 1993), and the third and fourth stratified the two previous ones for timing of death after infection by adding separate parameters before and after the 5th day of infection. These last two models therefore allowed to estimate a possible lag effect of infection on mortality. To apply weighting of individual patient days, model construction was based on a pooled logistic regression model that treated each patient day in the ICU as a single observation (the same approach was used for the models that generated the weights)(D'Agostino et al., 1990). All models were fitted using Generalised estimating equations (GEE) (Liang and Zeger, 1986), requiring an independent working correlation structure between repeated outcomes from the same patient (Vansteelandt, 2007). Models were also stratified for a categorical variable encoding the hospital or ICU that contributed data. All model construction and fitting was done using STATA v10's logistic command (STATA, 2007).

3.3 Results

For this study, 16 366 ICU admissions, contributing 108 328 ICU days of patients staying more than 2 days in the ICU were available for analysis. The median length of stay in ICU was 4 days, and for infected patients, the mean ICU stay prior to the first infection was 6 days. Of the 960 (5.9%) patients with one or more pneumonia-episodes, 277 (29%) died, compared to 1 524 deaths (9.9%) that occurred in 15 406 (94%) pneumonia-free patients. Of all pneumonia episodes 689, (73.8%) were associated with mechanical invasive ventilation. Of the 299 (1.8%) patients with one or more BSI episodes, 83 (5%) died, as compared to 1 594 deaths (9.9%) that occurred in 16 067 (98%) patients remaining BSI-free. Of all BSI episodes, 284 (95%) were associated with Central vascular catheter (CVC) use, while 195 (65%) were of primary (unknown or CVC) origin. Figure 3.1 shows data for the first

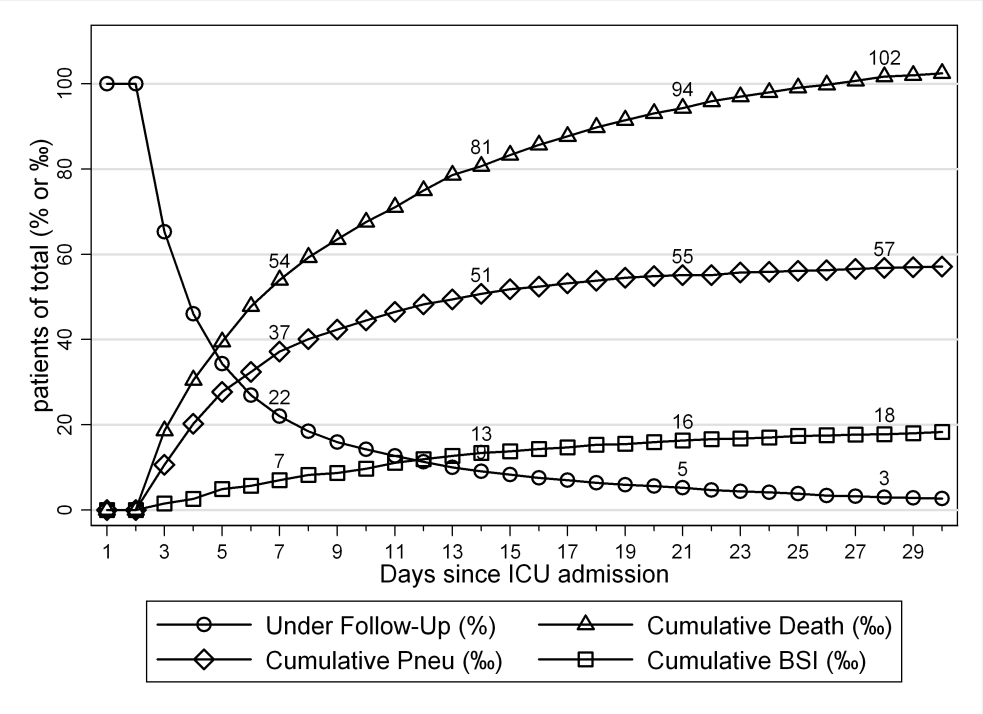


Figure 3.1: Evolution of patients under follow-up, with ICU-acquired pneumonia, ICU-acquired bloodstream infection and that died in the ICU during days 3-30; Percentages or per mils are calculated on the total of 16 366 patients admitted to ICU. Under Follow-up: % alive at the start of each day; Cumulative Death: ‰that died until particular day; Cumulative pneumonia: ‰with pneumonia until that day; Cumulative bloodstream infection: ‰of patients with bloodstream infection until that day.

30 days of ICU follow-up. Daily pneumonia, BSI and death rates were relatively stable throughout follow-up. It was found that at day 5, already 60% of the initial group had left the ICU, and 85% at day 20. This is indicative for the huge level of censoring taking place during the first days of ICU follow-up, and the need to adjust for this.

Tables 3.2-3.6 show the results of the multivariate models for the hazard of pneumonia, BSI, and censoring, used for calculation of IPE and IPC weights. The models for the hazard of pneumonia and BSI show that exposure to CVC, ventilation, intubation and prophylactic antibiotic use was associated with an increased risk for acquiring pneumonia, and that exposure to CVC, stoma, parenteral and tube feeding, intubation, and prophylactic and therapeutic antibiotic use was associated

with an increased risk for acquiring BSI. Besides the expected protective effect of SAPSII score category, the model for ICU discharge alive (censoring) shows protective effects for virtually all invasive device procedures and types of antibiotic use. This supports our consideration of time-varying exposure to therapeutic activity as a proxy for a patient's daily underlying health status, thus being indicative for worse prognosis (lengthening ICU stay).

Inspection of IPE weights revealed that these remained relatively stable, having a minimum-maximum range at 30 days of (0.1 to 9.5) with median 1.0 for pneumonia and (0.17 to 11.6) with median 1.0 for BSI. However, a subset of patients with very small predicted conditional probabilities of being discharged from the ICU yielded unstable IPC weights with range (1e-11 to 1e+19) and median 0.94. As shown in figure 3.2, the range of percentiles 1 to 99 of the combined IPE-IPC weights (infection and exposure) distribution remained fairly stable (relative to the large sample size) over the course of study lengths, having ranges (0.012 to 14.9) and (0.015 to 14.5) at 30 days for pneumonia and BSI respectively. Combined IPE-IPC weights were therefore truncated towards the above range, by setting the value of weights greater (lower) than percentile 99 (1) to the value of percentiles 99 (1) (Cole and Hernàn, 2008).

The MSPHMs for the attributable effect of infection on mortality were stratified on baseline confounders "age category", "SAPSII score category", "type of admission" and "antibiotic use at ICU admission". The model for the effect of pneumonia yielded a Hazard ratio (HR) of 1.1 [95% Confidence interval (CI) 0.76 to 1.5], while the model for the effect of BSI gave a HR 1.5 (95% CI 0.9 to 2.6) (Table 3.7). Stratifying the infection effect for SAPSII categories (Table 3.7, model 2) gave higher effects for the group of patients admitted with scores between 20-39 (intermediate category), and this for pneumonia (HR 2.3; 95% CI 1.4 to 3.8) and BSI (HR 3.4; 95% CI 1.4 to 7.9).

When looking at attributable mortality at different times since onset of infection (Table 3.7, model 3), we see a protective effect in the first 4 days after onset of pneumonia (0.59; 95% CI 0.3 to 1.1), and a stronger harmful effect from day 5 on (1.5; 95% CI 0.93 to 2.3). Such contrast was not found for BSI (1.4; 95% CI 0.78 to 2.5 versus 1.7; 95% CI 0.8 to 3.6). Furthermore, the aforementioned elevated effects

Risk factor	Categories	Adjusted hazard ratio (95% CI)		
		Pneumonia	Bloodstream infection	Discharge alive from ICU
Sex	Female vs Male	0.82 (0.71 to 0.94)**	n/a	n/a
Trauma	Yes vs No	1.55 (1.21 to 1.98)***	1.36 (0.89 to 2.07)	0.79 (0.72 to 0.88)***
Age category	40-59	n/a	0.77 (0.47 to 1.28)	0.97 (0.88 to 1.06)
	60-69	n/a	0.70 (0.42 to 1.18)	0.91 (0.82 to 1.01)
	70-74	n/a	0.95 (0.56 to 1.61)	0.87 (0.78 to 0.97)**
	75-79	n/a	0.86 (0.51 to 1.45)	0.86 (0.77 to 0.96)**
	≥80	n/a	0.56 (0.32 to 0.99)*	0.95 (0.85 to 1.05)
SAPS II score	20-39	n/a	n/a	0.83 (0.77 to 0.90)***
	40-59	n/a	n/a	0.67 (0.60 to 0.74)***
	≥60	n/a	n/a	0.56 (0.49 to 0.65)***
Type of admission	Scheduled surgery vs Medical adm.	0.96 (0.70 to 1.33)	n/a	1.16 (1.06 to 1.27)**
	Urgent surgery vs Medical adm.	1.25 (0.88 to 1.77)	n/a	1.10 (1.00 to 1.21)*

Table 3.2: Results for ICU admission variables (a) of construction of models for onset of pneumonia, bloodstream infection, and for discharge alive from ICU, used for calculating inverse probability of exposure and censoring weights, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; SAPS=Simplified acute physiology score; Effects for hospital or unit not shown; ICU=Intensive care unit; n/a: coefficient not used in the regression model (not applicable); *p-value<.05,**=p-value<.01,***p-value<.001 representing significance level from Wald-test.

Risk factor	Categories	Adjusted hazard ratio (95% CI)		
		Pneumonia	Bloodstream infection	Discharge alive from ICU
Prior surgery	Elective vs No surgery	1.18 (0.89 to 1.58)	n/a	n/a
	Urgent vs No surgery	0.90 (0.63 to 1.29)	n/a	n/a
Antibiotic use at admission	Prophylactic vs None	1.10 (0.86 to 1.40)	n/a	1.01 (0.92 to 1.12)
	Therapeutic vs None	0.95 (0.78 to 1.17)	n/a	0.97 (0.89 to 1.06)
	Both vs None	1.89 (0.99 to 3.61)	n/a	1.00 (0.64 to 1.56)
Infection at admission	Lower respiratory tract inf. vs None	n/a	1.38 (0.97 to 1.96)	0.90 (0.82 to 0.99)*
	Bloodstream inf. vs None	n/a	1.81 (0.95 to 3.42)	0.79 (0.66 to 0.96)*
	Other inf. vs None	n/a	1.59 (1.04 to 2.44)*	1.02 (0.91 to 1.14)
	Multiple inf. vs None	n/a	2.28 (1.25 to 4.15)**	0.88 (0.71 to 1.08)

Table 3.3: Results for ICU admission variables (b) of construction of models for onset of pneumonia, bloodstream infection, and for discharge alive from ICU, used for calculating inverse probability of exposure and censoring weights, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; Effects for hospital or unit not shown; ICU=Intensive care unit; n/a: coefficient not used in the regression model (not applicable); *p-value<.05,**=p-value<.01,***p-value<.001 representing significance level from Wald-test.

Risk factor	Type	Adjusted hazard ratio (95% CI)		
		Pneumonia	Bloodstream infection	Discharge alive from ICU
Day in ICU	Single	1.27 (1.20 to 1.35)***	1.25 (1.16 to 1.34)***	1.57 (1.52 to 1.61)***
	Quadratic	0.99 (0.99 to 1.00)***	0.99 (0.99 to 1.00)***	0.98 (0.98 to 0.98)***
Ventilation	Episode	1.91 (1.36 to 2.69)***	n/a	0.16 (0.14 to 0.20)***
	Ever	1.41 (1.06 to 1.88)*	n/a	1.23 (1.05 to 1.44)*
	Days	n/a	n/a	n/a
Central vascular catheter	Episode	n/a	2.46 (1.24 to 4.88)**	n/a
	Ever	3.10 (2.23 to 4.30)***	2.26 (0.90 to 5.68)	0.80 (0.74 to 0.87)***
	Days	0.96 (0.92 to 1.00)*	n/a	0.97 (0.95 to 0.98)***
Stoma feeding	Episode	n/a	1.54 (0.82 to 2.89)	0.69 (0.56 to 0.85)***
	Ever	n/a	n/a	n/a
	Days	n/a	n/a	n/a
Parenteral feeding	Episode	n/a	2.09 (1.56 to 2.80)***	0.50 (0.42 to 0.58)***
	Ever	1.43 (1.11 to 1.84)**	n/a	1.30 (1.11 to 1.53)***
	Days	0.97 (0.94 to 1.01)	n/a	n/a
Feeding through tube	Episode	1.65 (1.35 to 2.03)***	2.29 (1.46 to 3.59)***	0.56 (0.51 to 0.61)***
	Ever	n/a	0.61 (0.36 to 1.03)	1.09 (0.99 to 1.20)
	Days	0.96 (0.94 to 0.99)*	n/a	n/a

Table 3.4: Results for time-varying risk factors (a) of construction of models for onset of pneumonia, bloodstream infection, and for discharge alive from ICU, used for calculating inverse probability of exposure and censoring weights, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; Effects for hospital or unit not shown; n/a: coefficient not used in the regression model (not applicable); ICU=Intensive care unit; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; *p-value$<$.05,**=p-value$<$.01,***p-value$<$.001 representing significance level from Wald-test.

Risk factor	Type	Adjusted hazard ratio (95% CI)		
		Pneumonia	Bloodstream infection	Discharge alive from ICU
Feeding tube present	Episode	n/a	n/a	0.59 (0.54 to 0.65)***
	Ever	1.52 (1.22 to 1.88)***	n/a	n/a
	Days	1.02 (0.99 to 1.06)	n/a	1.03 (1.01 to 1.04)***
SDD antibiotic use	Episode	n/a	n/a	n/a
	Ever	n/a	n/a	1.42 (1.01 to 2.00)*
	Days	n/a	n/a	n/a
Profylactic antibiotic use	Episode	n/a	0.39 (0.22 to 0.70)**	n/a
	Ever	1.52 (1.22 to 1.90)***	n/a	n/a
	Days	n/a	n/a	1.11 (1.04 to 1.19)**
Therapeutic antibiotic use	Episode	n/a	0.44 (0.31 to 0.62)***	2.10 (1.79 to 2.46)***
	Ever	n/a	0.66 (0.43 to 1.03)	0.47 (0.40 to 0.56)***
	Days	n/a	n/a	1.11 (1.04 to 1.19)**
Any antibiotic use	Episode	0.33 (0.28 to 0.38)***	n/a	0.39 (0.35 to 0.43)***
	Ever	n/a	n/a	1.72 (1.52 to 1.94)***
	Days	n/a	n/a	0.91 (0.85 to 0.98)*

Table 3.5: Results for time-varying risk factors (b) of construction of models for onset of pneumonia, bloodstream infection, and for discharge alive from ICU, used for calculating inverse probability of exposure and censoring weights, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; Effects for hospital or unit not shown; SDD=selective digestive decontamination; ICU=Intensive care unit; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; n/a: coefficient not used in the regression model (not applicable); *p-value<.05,**=p-value<.01,***p-value<.001 representing significance level from Wald-test.

Risk factor	Type	Adjusted hazard ratio (95% CI)		
		Pneumonia	Bloodstream infection	Discharge alive from ICU
ICU-acquired pneumonia	Episode	n/a	n/a	n/a
	Ever	n/a	n/a	0.27 (0.21 to 0.34)***
	Days	n/a	n/a	1.1 (1.1 to 1.2)***
ICU-acquired bloodstream infection	Episode	n/a	n/a	n/a
	Ever	n/a	n/a	0.36 (0.23 to 0.57)***
	Days	n/a	n/a	1.1 (1.1 to 1.2)***

Table 3.6: Results for time-varying risk factors (c) of construction of models for onset of pneumonia, bloodstream infection, and for discharge alive from ICU, used for calculating inverse probability of exposure and censoring weights, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; Effects for hospital or unit not shown; ICU=Intensive care unit; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; n/a: coefficient not used in the regression model (not applicable); *p-value$<$.05,**=p-value$<$.01,***p-value$<$.001 representing significance level from Wald-test.

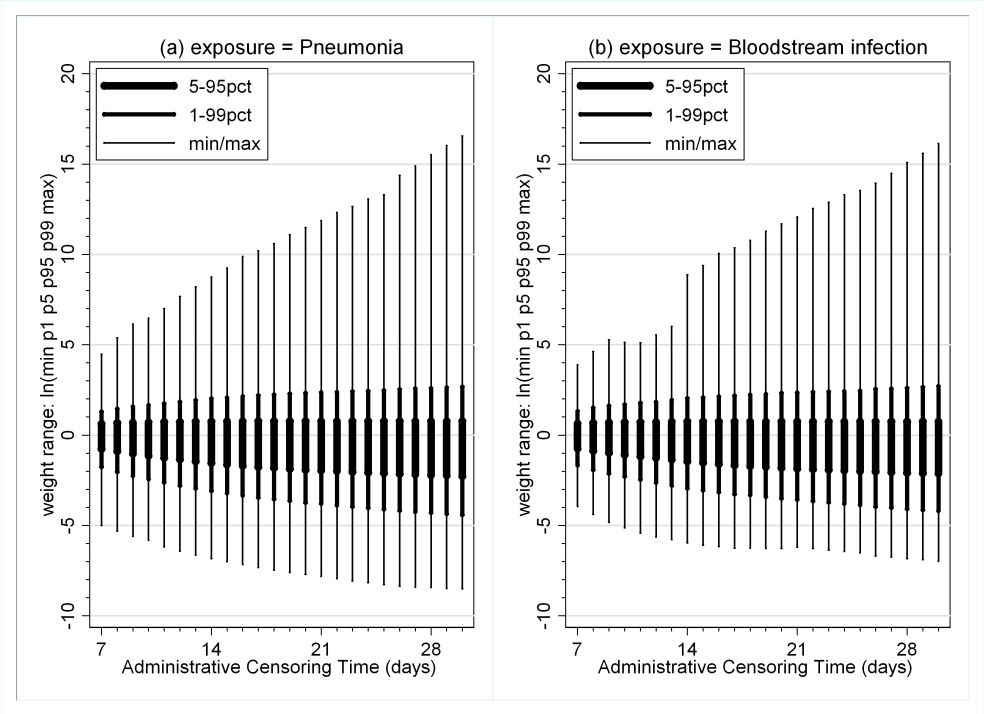


Figure 3.2: Daily distribution of combined inverse probability of infection (modelled separately for pneumonia and bloodstream infection) and censoring weight, through natural logarithms of percentiles 0, 1, 5, 95, 99, and 100.

	Bloodstream infection		Pneumonia	
	# (%)	Hazard ratio (95% CI)	# (%)	Hazard ratio (95% CI)
Model 1: overall infection effect				
ICU-acquired infection	299 (100.0)	1.6 (0.94 to 2.6)	934 (100.0)	1.1 (0.76 to 1.5)
Model 2: Infection x SAPS II score				
<20	17 (5.7)	2.2 (0.24 to 20)	74 (7.9)	1.3 (0.14 to 11)
20-39	112 (37.5)	3.4 (1.4 to 7.9)**	417 (44.6)	2.3 (1.4 to 3.8)**
40-59	108 (36.1)	1.4 (0.63 to 3.0)	305 (32.7)	0.90 (0.53 to 1.5)
≥ 60	62 (20.7)	1.1 (0.64 to 2.0)	138 (14.8)	0.71 (0.40 to 1.3)
Model 3: Infection x timing of death after infection				
Early[a]	99 (33.1)	1.4 (0.78 to 2.5)	212 (22.7)	0.59 (0.32 to 1.1)
Late[a]	200 (66.9)	1.7 (0.80 to 3.6)	722 (77.3)	1.5 (0.93 to 2.3)
Model 4: Infection x SAPS II score x timing of death after infection				
<20, Early	4 (1.3)	3.54 (0.37 to 33.83)	20 (2.1)	1.98 (0.21 to 18.37)
<20, Late	13 (4.3)	(no observed deaths)	54 (5.8)	0.14 (0.02 to 1.16)
20-39, Early	37 (12.4)	1.40 (0.41 to 4.85)	109 (11.7)	0.80 (0.28 to 2.28)
20-39, Late	75 (25.1)	6.48 (2.14 to 19.59)**	308 (33.0)	3.94 (1.96 to 7.90)**
40-59, Early	33 (11.0)	1.13 (0.37 to 3.44)	63 (6.7)	0.48 (0.21 to 1.09)
40-59, Late	75 (25.1)	1.55 (0.61 to 3.93)	242 (25.9)	1.23 (0.61 to 2.46)
≥ 60, Early	25 (8.4)	1.78 (0.87 to 3.64)	20 (2.1)	0.58 (0.18 to 1.85)
≥ 60, Late	37 (12.4)	0.81 (0.41 to 1.58)	118 (12.6)	0.84 (0.45 to 1.58)

Table 3.7: Attributable mortality effect Of ICU-acquired infection, using inverse probability of exposure and censoring weighted proportional hazards models, National surveillance Of ICU-acquired infections, Belgium, 2002-2003; ICU=Intensive care unit; CI=Confidence interval, # (%)=number (percentage of total) of infections falling within the category; Early: occurring within the first four days after onset of infection, Late: occurring after the fourth day after onset of infection; SAPS=Simplified acute physiology score; *p-value<.05, **p-value<.01, ***p-value<.001 represent significance level from Wald-test.

of pneumonia and BSI among patients with intermediate SAPSII scores were due to deaths occurring later after infection onset (Table 3.7, model 4).

Based on calculated predictions from the MSPHM for the overall attributable mortality effect, Figure 3.3 shows the estimated survival curves for the study population in the hypothetical scenarios where all patients acquire infection at day 3 in the ICU, as compared to when none of the patients acquires an infection. For the model having a monotonous effect of infection, only the curves of patient survival under exposure to BSI are clearly distinguishable and generally lower than those of the patient population under absence of BSI. For the model including lagged effects of infection, the survival curve for exposure to pneumonia crosses the

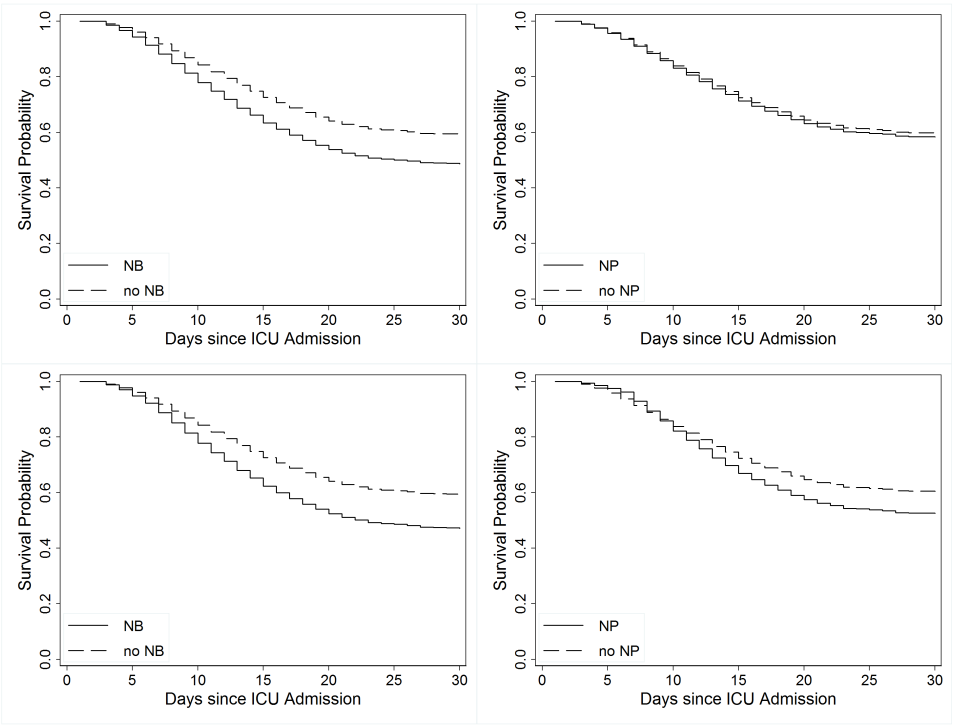


Figure 3.3: Predicted survival curves for the patient population hypothetically acquiring infection at day 3, and remaining infection-free; Left = effect of bloodstream infection; Right = effect of pneumonia; Upper = monotonous effect of infection from day 3; Lower = differential infection effect for days 3/6 and days 7/max after onset of infection; NB = nosocomial (ICU-acquired) bloodstream infection; NP = nosocomial pneumonia; ICU = intensive care unit.

curve for absence of pneumonia, which is indicative for the shift from protective to harmful exposure effects around day 7 in the ICU.

Finally, Appendix 3.5.2 gives a description and results of a sensitivity analysis in which the MSPHM is fitted repeatedly under varying administrative censoring times.

3.4 Discussion

This article describes the estimation of the attributable effect of ICU-acquired infection on the risk for mortality using Inverse probability of exposure and censoring weighted (IPECW) estimation under a MSPHM (Hernàn et al., 2001). Our analysis showed a neutral risk of mortality for ICU-acquired pneumonia, and a marginally higher risk for mortality for ICU-acquired BSI. Our analysis also demonstrated that pneumonia had a marginally higher effect on mortality after the fourth day of infection that was in contrast to a protective effect during the first 4 days, which is an inversion that was not seen for BSI. For both infection types, the group of patients with intermediate SAPSII scores contributed the highest mortality effects, both infection types consistently later after infection onset.

To our knowledge, the study presented here is among the few to analyse effects of infections in a national multicentric setting, and also among the first to use weighted adjustment for time-dependent confounding and informative censoring explained by measured time-varying prognostic factors in the setting of ICU survival. The use of this method must be seen in light of recent calls (Lambert et al., 2011; Muscedere, 2009; Timsit et al., 2011) for using estimation techniques that can adequately deal with the methodological pitfalls when estimating attributable outcome of infection. Adjustment was made by weighting because stratification for so-called intermediate time-varying confounders that act both as causes and effects of exposure to infection will induce non-causal associations between infection and mortality (Hernàn et al., 2001; Robins, 2000). Moreover, while risk ratio estimates from stratified methods have interpretation conditional on distinct levels of time-dependent and -independent confounders, the marginal structural model yields a causal estimate of the marginal (over time-dependent confounders) risk ratio, which is more relevant for public health purposes.

Our model's neutral overall attributable effect of pneumonia on mortality, although differently obtained and interpreted, is in line with reports using conventional stratification-based methods but similarly relying on extensive adjustment for time-independent and -dependent confounders (Heyland et al., 1999; Papazian et al., 1996; Timsit et al., 1996; Kollef et al., 1995). It is also in line with results from

randomised trials for the prevention of pneumonia (mostly ventilator-associated) that demonstrated a decrease in infection incidence but without altering ICU mortality (Muscedere et al., 2010). For BSI, a higher but still statistically non-significant effect was found. Earlier reports on the effect of primary CVC-related BSIs found mostly risk increasing but statistically insignificant effects individually (Digiovine et al., 1999; Rello et al., 2000; Renaud and Brun-Buisson, 2001; Soufir et al., 1999), which turned significant when aggregated into a meta-analysis (Siempos et al., 2009). Of note is that a study by Renaud and Brun-Buisson (2001) showed a higher attributable mortality effect for secondary BSI, which might explain the slightly higher attributable mortality of our study (including primary and secondary BSI). The higher attributable mortality among patients with intermediate SAPSII scores was also previously reported, for both pneumonia and BSI (Bekaert et al., 2011; Kim et al., 2005; Nguile-Makao et al., 2010).

Our results show that pneumonia and BSI behave differently in terms of the variation of the post-infection attributable hazard for mortality, with the former showing protective risk immediately and harmful risk only longer after onset, but the latter instead showing harmful effects both immediately and later after onset. The phenomenon as observed for pneumonia of a progressively increased risk for mortality once an infection is observed was recently also reported for Ventilator-associated pneumonia (VAP) (Bekaert et al., 2011). It also explains some of the more harmful attributable effect estimates for pneumonia in other reports that used follow-up periods up to and above 100 days (Bercault and Boulain, 2001; Nguile-Makao et al., 2010; Wolkewitz et al., 2009) as compared to the period of 30 days that we used here. Such studies with a higher length of follow-up will not only observe more deaths in the total study population, but also progressively more in later periods among infected patients if we extrapolate the increasingly harmful mortality effect late after infection onset.

The following limitations have to be taken into account when interpreting this study's results: first, we had no info on the adequateness of the appropriate treatment of the studied infections. This would be an added value, specifically when studying attributable mortality effects early and late after infection onset. Second, in relation to the previous argument, the design of a prospective surveillance study

for HAI might in itself have contributed to a more neutral effect on mortality, due to the fact that any infected patient under surveillance might benefit from the increased attention towards the targeted types of infection. Third, time-dependent confounders were limited to daily use of invasive devices and antimicrobial therapy, no organ dysfunction score were used for adjustment but these might have contributed to a finer adjustment. Finally, our analysis suffered from the strong association of invasive devices with probability of remaining in the ICU, leading to highly variable and unstable IPC weights, and as a consequence wide confidence intervals. Future research projects might investigate alternative methods for such IPC weights, or techniques to make the analysis more optimal.

3.5 Appendix

3.5.1 Calculating the inverse probability weights

The MSPHM applies IPE weights to adjust for time-dependent confounders of the infection-mortality association, and IPC weights to adjust for selective dropout of patients being discharged alive before the administrative censoring date of 30 days. Exposure weights are the inverse of a patient's daily probability of having acquired his or her observed infection-exposure until that day, conditional on confounder history until then. These are derived by constructing a proportional hazards model for the hazard of infection that includes the history of time-dependent and baseline (time-independent) confounders for the infection-mortality association, and by using the fitted model to calculate predictions of the conditional probability of acquiring infection at each day. An IPE weight at day t is therefore the reciprocal of the estimated risk of acquiring infection at that day (or staying free of infection, depending on the observed infection-status) multiplied from day 1 to t. A numerator is calculated to make the weights more stable, and was constructed similarly, except that the regression model only used time-independent confounders. The construction of IPC weights is similar to that of IPE weights, except that now proportional hazard models for censoring (defined as discharged alive from the ICU) were constructed and used for predictions. A IPC weight at each particular

day is informally the reciprocal of a patient's probability of remaining in the ICU until that day, given his or her time-dependent and -independent history (including information on the infection status) up to that day.

All proportional hazard models are based on a pooled logistic regression model that treated each patient day in the ICU as a single observation (D'Agostino et al., 1990). Separate models were created for pneumonia and BSI, these only incorporate the 1st possible infection episode for each patient. All models were fitted using GEE (Liang and Zeger, 1986), using an independent working correlation structure between repeated outcomes from the same patient. Models were also stratified for a categorical variable encoding the hospital or ICU that contributed data. All model construction and fitting was done using STATA's logistic (STATA, 2007) command.

Construction of the models for calculating the IPE and IPC weights starts with identifying risk factors for infection, discharge alive from ICU and ICU-mortality, and thus potential confounding factors for the infection-mortality and censoring-mortality associations. Univariate models were therefore constructed for any of the outcomes described above having any risk factor as a single predictor. Tables 3.8-3.12 show results from this analysis for time-independent factors (variables collected at ICU admission) and time-dependent factors respectively. From Tables 3.10-3.12 we see that virtually all time-dependent invasive device exposures are individually strongly predictive for staying in the ICU. Those risk factors having an observed Wald test significance level of less than 0.05 were consequently used in a stepwise backward removal procedure with significance level 0.1 in the models for the prediction of inverse probability weights.

The constructed models for the hazard of pneumonia, BSI and discharge alive from the ICU were used to calculate for each patient day the conditional probability of acquiring any of the above outcomes. The probabilities of acquiring infection were converted towards the probability of the actual infection status at each day, by subtracting the predicted probability from 1 in case of absence of infection. Likewise, the conditional probability of remaining in the ICU was obtained by subtracting the probabilities of discharge alive in the ICU from 1. The estimated probabilities from day 1 to each particular day are multiplied to obtain the probability of actual infection status and of remaining in the ICU up to each

Risk factor	Category	Patients	Patient days	Hazard ratio (95% CI)			
		(%)	(%)	Pneumonia	Bloodstream infection	ICU mortality	Discharge alive from ICU
Acute coronary care	No	13191 (78%)	90532 (81%)				
	Yes	3678 (22%)	20710 (19%)	0.75 (0.62 to 0.91)**	0.90 (0.65 to 1.25)	1.17 (1.03 to 1.33)*	1.29 (1.23 to 1.35)***
Age category	<40	1204 (7%)	7913 (7%)				
	40-59	3294 (20%)	21612 (19%)	0.97 (0.73 to 1.28)	0.92 (0.57 to 1.48)	2.34 (1.67 to 3.29)***	0.95 (0.88 to 1.03)
	60-69	3349 (20%)	22542 (20%)	1.03 (0.79 to 1.36)	0.79 (0.49 to 1.28)	2.53 (1.81 to 3.54)***	0.90 (0.83 to 0.97)**
	70-74	2617 (16%)	17787 (16%)	1.03 (0.78 to 1.37)	1.15 (0.72 to 1.85)	2.89 (2.07 to 4.05)***	0.87 (0.80 to 0.94)***
	75-79	2995 (18%)	20710 (19%)	0.95 (0.72 to 1.25)	1.04 (0.65 to 1.67)	3.30 (2.37 to 4.60)***	0.82 (0.76 to 0.89)***
	≥80	3410 (20%)	20678 (19%)	0.77 (0.57 to 1.02)	0.58 (0.34 to 0.99)*	4.80 (3.46 to 6.67)***	0.93 (0.86 to 1.01)
AB use before admission	None	9709 (58%)	59812 (54%)				
	Prophylactic	4296 (25%)	25477 (23%)	2.44 (2.10 to 2.83)***	1.12 (0.83 to 1.51)	0.52 (0.45 to 0.61)***	1.15 (1.10 to 1.21)***
	Therapeutic	2815 (17%)	25471 (23%)	0.95 (0.80 to 1.13)	1.40 (1.08 to 1.82)*	0.97 (0.87 to 1.09)	0.55 (0.52 to 0.58)***
	Both	49 (0%)	482 (0%)	3.87 (2.10 to 7.14)***	1.91 (0.56 to 6.58)	0.92 (0.46 to 1.82)	0.52 (0.37 to 0.74)***
Infection at admission	None	12481 (74%)	73201 (66%)				
	LRT	2553 (15%)	22762 (20%)	0.62 (0.52 to 0.73)***	1.14 (0.87 to 1.51)	1.54 (1.38 to 1.73)***	0.47 (0.45 to 0.50)***
	BSI	310 (2%)	2864 (3%)	0.47 (0.29 to 0.76)**	1.49 (0.84 to 2.64)	1.49 (1.15 to 1.93)**	0.44 (0.38 to 0.51)***
	Other	1320 (8%)	10313 (9%)	0.52 (0.40 to 0.68)***	1.35 (0.94 to 1.93)	1.05 (0.88 to 1.26)	0.65 (0.60 to 0.69)***
	Multiple	205 (1%)	2102 (2%)	0.85 (0.56 to 1.31)	2.16 (1.26 to 3.70)**	1.32 (0.96 to 1.81)	0.39 (0.33 to 0.47)***

Table 3.8: Univariate analysis of time independent risk factors (a) for the onset of ICU-acquired pneumonia, bloodstream infection, and of mortality and discharge alive from ICU; ICU=Intensive care unit; Patient(day)s (%)=the number (percentage of total) of patient(day)s within the corresponding risk factor level; Hazard ratio=derived from proportional hazards models for the indicated outcome (pneumonia, bloodstream infection, mortality, discharge alive from ICU) having the corresponding risk factor as single predictor; CI=Confidence Interval; AB=Antibiotic; LRT=Lower respiratory tract; BSI=Bloodstream infection; *p-value<.05, **p-value<.01, ***p-value<.001 represent significance level from Wald-test.

Risk factor	Category	Patients	Patient days	Hazard ratio (95% CI)			
		(%)	(%)	Pneumonia	Bloodstream infection	ICU mortality	Discharge alive from ICU
Prior surgery	None	9996 (59%)	65598 (59%)				
	Elective	4824 (29%)	28221 (25%)	2.01 (1.73 to 2.33)***	1.11 (0.83 to 1.47)	0.46 (0.40 to 0.53)***	1.32 (1.26 to 1.38)***
	Urgent	2049 (12%)	17423 (16%)	1.81 (1.53 to 2.14)***	1.43 (1.08 to 1.91)*	0.77 (0.67 to 0.88)***	0.72 (0.68 to 0.77)***
SAPS II score	<20	2910 (17%)	13734 (12%)				
	20-39	9300 (55%)	54930 (49%)	1.26 (0.98 to 1.62)	1.30 (0.78 to 2.18)	4.07 (2.68 to 6.18)***	0.68 (0.64 to 0.71)***
	40-59	3365 (20%)	29396 (26%)	1.48 (1.14 to 1.91)**	1.76 (1.04 to 2.96)*	10.35 (6.82 to 15.71)***	0.32 (0.30 to 0.34)***
	>=60	1294 (8%)	13182 (12%)	1.40 (1.05 to 1.87)*	2.02 (1.16 to 3.51)*	19.15 (12.56 to 29.18)***	0.17 (0.16 to 0.19)***
Sex	Male	9929 (59%)	66550 (60%)				
	Female	6940 (41%)	44692 (40%)	0.75 (0.66 to 0.87)***	0.92 (0.73 to 1.16)	1.06 (0.96 to 1.17)	1.05 (1.01 to 1.09)**
Trauma	No	15851 (94%)	103141 (93%)				
	Yes	1018 (6%)	8101 (7%)	1.78 (1.46 to 2.18)***	1.43 (1.00 to 2.05)	0.71 (0.57 to 0.88)**	0.80 (0.74 to 0.86)***
Type of admission	Medical	10352 (61%)	69104 (62%)				
	Sched. surg.	4447 (26%)	24692 (22%)	2.03 (1.74 to 2.37)***	0.95 (0.70 to 1.29)	0.36 (0.31 to 0.43)***	1.48 (1.42 to 1.55)***
	Unsched. surg.	2070 (12%)	17446 (16%)	1.92 (1.63 to 2.26)***	1.19 (0.89 to 1.59)	0.72 (0.63 to 0.82)***	0.76 (0.72 to 0.81)***

Table 3.9: Univariate analysis of time independent risk factors (b) for the onset of ICU-acquired pneumonia, bloodstream infection, and of mortality and discharge alive from ICU; ICU=Intensive care unit; Patient(day)s (%)=the number (percentage of total) of patient(day)s within the corresponding risk factor level; Hazard ratio=derived from proportional hazards models for the indicated outcome (pneumonia, bloodstream infection, mortality, discharge alive from ICU) having the corresponding risk factor as single predictor; CI=Confidence Interval; SAPS=Simplified acute physiology score; *p-value<.05, **p-value<.01, ***p-value<.001 represent significance level from Wald-test.

Risk factor	Type	Patients	Patient days	Hazard ratio (95% CI)			
		(%)	(%)	Pneumonia	Bloodstream infection	ICU mortality	Discharge alive from ICU
Ventilation	Episode	10586 (63%)	76902 (69%)	3.84 (3.07 to 4.81)***	4.36 (2.74 to 6.94)***	1.17 (1.04 to 1.33)*	0.37 (0.36 to 0.39)***
	Ever		81387 (73%)	5.64 (4.32 to 7.36)***	6.01 (3.31 to 10.94)***	1.86 (1.59 to 2.19)***	0.42 (0.40 to 0.43)***
	Days			1.11 (1.06 to 1.16)***	1.13 (1.05 to 1.21)**	1.03 (1.02 to 1.05)***	0.86 (0.85 to 0.87)***
CVC	Episode	7440 (44%)	44625 (40%)	2.83 (2.44 to 3.29)***	1.81 (1.39 to 2.36)***	1.88 (1.69 to 2.10)***	0.03 (0.03 to 0.03)***
	Ever		65284 (59%)	4.56 (3.73 to 5.57)***	2.54 (1.74 to 3.70)***	2.53 (2.19 to 2.92)***	0.32 (0.31 to 0.34)***
	Days			1.11 (1.08 to 1.14)***	1.04 (1.01 to 1.07)**	1.05 (1.04 to 1.07)***	0.77 (0.76 to 0.78)***
Stoma feeding	Episode	304 (2%)	2380 (2%)	0.69 (0.41 to 1.15)	1.58 (0.92 to 2.71)	0.55 (0.37 to 0.81)**	0.58 (0.50 to 0.68)***
	Ever		2687 (2%)	0.70 (0.43 to 1.15)	1.47 (0.86 to 2.49)	0.58 (0.41 to 0.83)**	0.66 (0.58 to 0.76)***
	Days			0.96 (0.89 to 1.02)	1.03 (0.99 to 1.09)	0.95 (0.91 to 0.99)**	0.98 (0.96 to 0.99) **
Parenteral feeding	Episode	2527 (15%)	18930 (17%)	1.02 (0.86 to 1.21)	2.09 (1.61 to 2.69)***	0.73 (0.64 to 0.82)***	0.35 (0.32 to 0.37)***
	Ever		24243 (22%)	1.03 (0.87 to 1.21)	1.90 (1.45 to 2.49)***	0.83 (0.74 to 0.94)**	0.43 (0.41 to 0.46)***
	Days			0.97 (0.95 to 0.99)**	1.03 (1.01 to 1.06)**	0.99 (0.97 to 1.00)**	0.91 (0.90 to 0.92)***
Feeding through tube	Episode	5956 (35%)	39804 (36%)	2.30 (1.99 to 2.67)***	1.93 (1.49 to 2.51)***	1.10 (0.99 to 1.22)	0.15 (0.14 to 0.16)***
	Ever		51335 (46%)	2.47 (2.11 to 2.91)***	1.71 (1.27 to 2.30)***	1.20 (1.08 to 1.34)***	0.44 (0.42 to 0.46)***
	Days			1.05 (1.03 to 1.07)***	1.02 (0.99 to 1.04)	1.01 (1.00 to 1.02)*	0.87 (0.86 to 0.87)***
Feeding tube present	Episode	4873 (29%)	36372 (33%)	2.27 (1.96 to 2.63)***	1.25 (0.97 to 1.61)	0.99 (0.89 to 1.11)	0.16 (0.14 to 0.17)***
	Ever		46003 (41%)	2.48 (2.12 to 2.91)***	1.26 (0.95 to 1.67)	1.22 (1.09 to 1.37)***	0.34 (0.33 to 0.36)***
	Days			1.07 (1.05 to 1.09)***	0.99 (0.96 to 1.01)	1.00 (0.99 to 1.02)	0.86 (0.85 to 0.87)***

Table 3.10: Univariate analysis of time dependent risk factors (a) for the onset of ICU-acquired pneumonia, bloodstream infection, and of mortality and discharge alive from ICU; ICU=Intensive care unit; Patient(day)s (%)=the number (percentage of total) of patient(day)s within the corresponding risk factor level; Hazard ratio=derived from proportional hazards models for the indicated outcome (pneumonia, bloodstream infection, mortality, discharge alive from ICU) having the corresponding risk factor as single predictor; CI=Confidence Interval; CVC=Central vascular catheter; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; *p-value<.05, **p-value<.01, ***p-value<.001 represent significance level from Wald-test.

Risk factor	Type	Patients	Patient days	Hazard ratio (95% CI)			
		(%)	(%)	Pneumonia	Bloodstream infection	ICU mortality	Discharge alive from ICU
SDD antibiotic use	Episode	129 (1%)	775 (1%)	0.93 (0.45 to 1.92)	1.09 (0.34 to 3.52)	0.94 (0.55 to 1.62)	0.16 (0.10 to 0.25)***
	Ever		1226 (1%)	1.21 (0.69 to 2.12)	0.65 (0.20 to 2.09)	1.08 (0.73 to 1.62)	0.54 (0.45 to 0.66)***
	Days			0.98 (0.91 to 1.06)	0.95 (0.84 to 1.08)	1.01 (0.97 to 1.05)	0.92 (0.89 to 0.95)***
Profylactic antibiotic use	Episode	4917 (29%)	11349 (10%)	1.53 (1.23 to 1.89)***	0.98 (0.57 to 1.66)	0.44 (0.33 to 0.60)***	0.47 (0.44 to 0.50)***
	Ever		29383 (26%)	2.76 (2.41 to 3.16)***	1.11 (0.86 to 1.44)	0.58 (0.51 to 0.66)***	1.33 (1.27 to 1.38)***
	Days			1.12 (1.09 to 1.15)***	1.01 (0.95 to 1.07)	0.90 (0.85 to 0.94)***	1.06 (1.04 to 1.08)***
Therapeutic antibiotic use	Episode	6760 (40%)	51786 (47%)	0.44 (0.38 to 0.51)***	0.65 (0.51 to 0.84)***	0.81 (0.73 to 0.90)***	0.31 (0.30 to 0.33)***
	Ever		60029 (54%)	0.46 (0.39 to 0.54)***	0.77 (0.57 to 1.04)	1.34 (1.18 to 1.53)***	0.31 (0.29 to 0.32)***
	Days			0.91 (0.89 to 0.93)***	0.98 (0.96 to 1.00)	1.01 (1.00 to 1.02)	0.86 (0.85 to 0.87)***
Any antibiotic use	Episode	10853 (64%)	63147 (57%)	0.54 (0.47 to 0.63)***	0.67 (0.52 to 0.85)***	0.71 (0.64 to 0.79)***	0.29 (0.28 to 0.30)***
	Ever		81004 (73%)	1.48 (1.22 to 1.79)***	1.09 (0.76 to 1.58)	0.98 (0.85 to 1.12)	0.50 (0.48 to 0.52)***
	Days			0.93 (0.92 to 0.95)***	0.98 (0.95 to 1.01)	0.99 (0.98 to 1.01)	0.86 (0.85 to 0.87)***
Tracheotomy intubation	Episode	716 (4%)	6869 (6%)	0.96 (0.72 to 1.28)	1.03 (0.71 to 1.49)	0.36 (0.28 to 0.45)***	0.33 (0.29 to 0.38)***
	Ever		7489 (7%)	0.94 (0.71 to 1.24)	1.09 (0.77 to 1.55)	0.45 (0.37 to 0.55)***	0.47 (0.42 to 0.52)***
	Days			1.00 (0.97 to 1.04)	1.00 (0.96 to 1.03)	0.96 (0.93 to 0.98)***	0.96 (0.95 to 0.98)***
Nasal intubation	Episode	224 (1%)	870 (1%)	1.76 (0.98 to 3.14)	2.59 (1.15 to 5.85)*	1.41 (0.88 to 2.24)	0.19 (0.12 to 0.29)***
	Ever		1832 (2%)	1.30 (0.81 to 2.11)	2.34 (1.30 to 4.22)**	0.81 (0.53 to 1.22)	0.79 (0.67 to 0.92)**
	Days			1.03 (0.96 to 1.10)	1.08 (1.01 to 1.15)*	0.99 (0.93 to 1.04)	0.93 (0.90 to 0.96)***

Table 3.11: Univariate analysis of time dependent risk factors (b) for the onset of ICU-acquired pneumonia, bloodstream infection, and of mortality and discharge alive from ICU; ICU=Intensive care unit; Patient(day)s (%)=the number (percentage of total) of patient(day)s within the corresponding risk factor level; Hazard ratio=derived from proportional hazards models for the indicated outcome (pneumonia, bloodstream infection, mortality, discharge alive from ICU) having the corresponding risk factor as single predictor; CI=Confidence Interval; SDD=selective digestive decontamination; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; *p-value<.05, **p-value<.01, ***p-value<.001 represent significance level from Wald-test.

Risk Factor	Type	Patients	Patient days	Hazard ratio (95% CI)			
		(%)	(%)	Pneumonia	Bloodstream infection	ICU mortality	Discharge alive from ICU
Oral intubation	Episode	6914 (41%)	37865 (34%)	2.51 (2.18 to 2.89)***	1.64 (1.29 to 2.09)***	2.21 (2.00 to 2.45)***	0.03 (0.02 to 0.03)***
	Ever		60675 (55%)	3.63 (3.02 to 4.36)***	2.01 (1.45 to 2.79)***	2.48 (2.17 to 2.83)***	0.35 (0.34 to 0.37)***
	Days			1.07 (1.04 to 1.09)***	1.03 (1.00 to 1.05)*	1.06 (1.05 to 1.08)***	0.78 (0.77 to 0.79)***
Any intubation	Episode	7287 (43%)	45178 (41%)	2.66 (2.29 to 3.09)***	1.75 (1.34 to 2.29)***	1.87 (1.67 to 2.09)***	0.04 (0.03 to 0.04)***
	Ever		64113 (58%)	4.15 (3.42 to 5.05)***	2.89 (1.98 to 4.21)***	2.48 (2.15 to 2.86)***	0.33 (0.31 to 0.34)***
	Days			1.08 (1.05 to 1.12)***	1.04 (1.01 to 1.07)**	1.05 (1.04 to 1.07)***	0.78 (0.77 to 0.79)***
Surgery	Episode	1486 (9%)	1788 (2%)	1.50 (0.97 to 2.33)	1.81 (0.90 to 3.66)	0.41 (0.22 to 0.77)**	0.14 (0.10 to 0.19)***
	Ever		12475 (11%)	1.79 (1.48 to 2.17)***	1.40 (1.04 to 1.89)*	0.81 (0.70 to 0.95)**	0.66 (0.61 to 0.71)***
	Days			1.32 (1.17 to 1.49)***	1.19 (1.01 to 1.40)*	0.84 (0.75 to 0.94)**	0.71 (0.67 to 0.75)***
ICU-acquired pneumonia	Ever	966 (6%)	10768 (10%)		1.41 (1.05 to 1.91)*	0.68 (0.59 to 0.79)***	0.35 (0.32 to 0.38)***
	Days			1.02 (0.99 to 1.05)		0.98 (0.96 to 0.99)**	0.93 (0.92 to 0.94)***
ICU-acquired bloodstream infection	Ever	322 (2%)	2797 (3%)		0.87 (0.54 to 1.40)	1.19 (0.94 to 1.51)	0.47 (0.39 to 0.55)***
	Days			0.99 (0.92 to 1.06)		1.01 (0.98 to 1.04)	0.96 (0.93 to 0.99)**

Table 3.12: Univariate analysis of time dependent risk factors (c) for the onset of ICU-acquired pneumonia, bloodstream infection, and of mortality and discharge alive from ICU; ICU=Intensive care unit; Patient(day)s (%)=the number (percentage of total) of patient(day)s within the corresponding risk factor level; Hazard ratio=derived from proportional hazards models for the indicated outcome (pneumonia, bloodstream infection, mortality, discharge alive from ICU) having the corresponding risk factor as single predictor; CI=Confidence Interval; Episode/Ever/Days=type by which the risk factor was coded: Episode=exposure can be set to 0 after being set to 1, Ever=monotonous exposure (once exposed, the patient remains so until ICU discharge), Days=cumulative exposure; *p-value<.05,**p-value<.01,***p-value<.001 represent significance level from Wald-test.

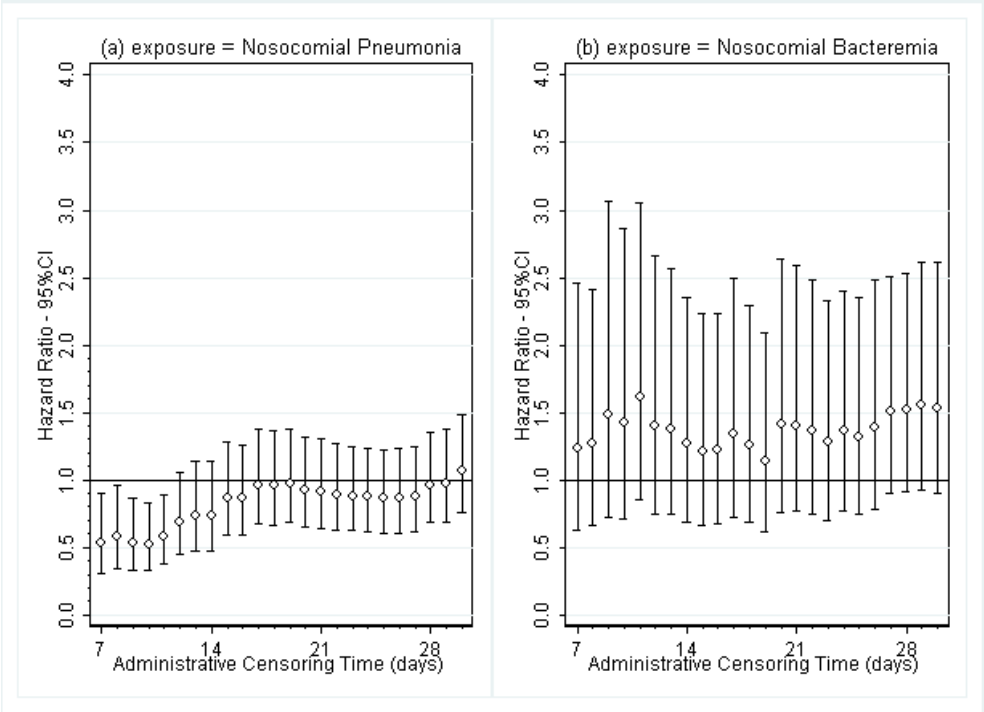


Figure 3.4: Hazard for mortality ratio of ICU-acquired pneumonia infected (a) and ICU-acquired bloodstream infection infected (b) versus uninfected patients using a Marginal structural proportional hazards model with varying administrative censoring times.

particular patient day. IPE and IPC were then created by inverting the conditional probabilities of actual infection status and of remaining in the ICU up to each day respectively. These were multiplied with each other to represent the daily combined IPE-IPC weights. Finally, these were stabilised by division by combined IPE-IPC weights derived from the same models for acquiring infection and being discharged alive from the ICU but not containing time-dependent confounders as predictors.

Because separate models were used for modelling the risk of acquiring pneumonia and BSI, separate combined weights sets were obtained for these two infection types.

3.5.2 Sensitivity analysis

Because the MSPHM is fit on data where each patient-day is weighted for its inverse probability of not being censored, or of staying alive in the ICU, it infers the HAI-effect that would have been observed if the ICU population was not discharged before the end of follow-up date. To investigate the robustness of the model's estimates to the follow-up period, we fitted the MSPHM repeatedly under varying end of follow-up or administrative censoring times: for example, when implementing an administrative censoring at 15 days, the same number of patients will be used in the analysis but their ICU follow-up will be truncated to 15 days. Figure 3.4 shows the effect of applying various administrative censoring times on the results of the MSPHM for the effects of pneumonia and BSI on mortality. When decreasing the study time from 30 to 5 days, the pneumonia effect remained more or less neutral until day 15, around which the HR shifts to protective values of 0.55 at times 7-10. The graph for BSI did not show this decline at lower follow-up times. For the two infection types, this different behavior of attributable mortality for varying follow-up times was directly related to the different attributable mortality early and late after infection onset of infection (as reported in the main paper). Pneumonia are protective for mortality early after onset, but have more harmful attributable mortality late after onset, implying that the longer the follow-up time, the more this "lag" effect of pneumonia can play a role. For BSI, no apparent contrast was seen early and late after onset of infection. The fairly wide confidence intervals (despite the large sample size) are due to the wide range of IPC-weights that were used to correct this model, which was caused by the strong associations between time-dependent confounders and the censoring event "discharge alive".

CHAPTER 4

Marginal structural models for partial exposure regimes

This chapter is based on the following article: Vansteelandt, S., Mertens, K., Suetens, C. and Goetghebeur, E. (2009) "Marginal structural models for partial exposure regimes," *Biostatistics*, 10(1): 46-59.

Summary

Intensive care unit (ICU) patients are highly susceptible to Healthcare-associated infection (HAI) due to their poor health and many invasive therapeutic treatments. The effect on mortality of acquiring such infections is, however, poorly understood. Our goal is to quantify this using data from the National surveillance of infections acquired in intensive care units (NSIH-ICU) (Belgium). This is challenging because of the presence of time-dependent confounders, such as mechanical ventilation, which lie on the causal path from infection to mortality. Standard statistical analyses may be severely misleading in such settings and have shown contradictory results. Inverse probability weighting for marginal structural models may instead be used, but is not directly applicable because these models parametrise the effect

of acquiring infection on a given day in ICU, versus *never* acquiring infection in ICU, and this is ill-defined when ICU discharge precedes that day. Additional complications arise from informative censoring of the survival time by hospital discharge, and from the instability of the inverse weighting estimation procedure. We accommodate this by introducing a new class of marginal structural models for so-called partial exposure regimes. These describe the effect on the hazard of death of acquiring infection on a given day s, versus not acquiring infection *up to that day*, had patients stayed in the ICU for at least s days.

4.1 Introduction

ICU patients are estimated to have a 5 to 10 times higher risk of acquiring nosocomial, i.e. hospital-acquired, infections than patients in other hospital units, due to their poor health and many invasive therapeutic treatments. These infections are believed to account for 50% of all major complications of hospitalisation and are considered to have a substantial impact on morbidity, mortality and medical costs (Gaynes, 1997). In 1985, the Study on the Efficacy of Nosocomial Infection Control (Haley et al., 1985) demonstrated that surveillance of nosocomial infections can reduce infection rates by as much as 30%, provided that sufficient infection control staff and adequate surveillance are available. Since then, surveillance of nosocomial infections has played a fundamental role in assessing and improving the quality of medical care.

In 1995, the Scientific Institute of Public Health (Belgium) set up a national surveillance network in ICUs in collaboration with the Belgian Society for Intensive Care and Emergency Medicine (Suetens et al., 1999). The aim of this network is twofold: to assist individual ICUs to obtain local incidence statistics for the main nosocomial infections ICU-acquired pneumonia and Bloodstream infection (BSI); and to offer national statistics in parallel to guide the interpretation of each ICU's performance. Surveillance and the definition of infections that we will adopt follow a standard protocol based on a Europe-wide consensus reached in the Hospitals in Europe link for infection control through surveillance (HELICS) project (Suetens

et al., 2003).

In this article, we will use data collected through the network to quantify the effect of ICU-acquired pneumonia on mortality in ICU patients. This is a complex problem for various reasons. First, the association between infection and mortality is disturbed by time-dependent confounders. For instance, daily exposure to invasive treatments such as mechanical ventilation or the presence of a central vascular catheter increases the risk of infection, and the poor health conditions leading to these treatments are also indicative of an increased mortality risk. These confounders lie on the causal path from infection to mortality because infection makes it more likely that the patient will receive invasive therapeutic treatments. Standard adjustment approaches, such as time-dependent proportional hazards regression, will then usually give biased results [see, for example, Andersen (1986); Bryan et al. (2004); Kalbfleisch and Prentice (2002); Robins (1986, 1997, 2000); Vansteelandt (2007)] Second, the censoring of the survival time upon hospital discharge may be informative because the decision to discharge patients is closely related to their health status, so that mortality rates may differ substantially between those who are discharged on a given day and those who are not.

The problem of estimating the mortality rate attributable to ICU-acquired infection has received much attention in the intensive care literature [see e.g. Carlet (2001); Vincent (2003); Schumacher et al. (2007)], as a reliable estimate is not only of theoretical interest but also important for determinining the potential benefits of new drugs. Common practice is to fit logistic regression models for mortality in ICU, adjusting for pneumonia status upon ICU discharge, for length of stay in ICU, and possibly for time-dependent variables measured prior to infection. An alternative approach is to base inference on proportional hazards models for time to death, adjusting for either infection status upon ICU discharge or time-dependent infection status, and additionally for time-dependent variables measured prior to infection. These analyses ignore the aforementioned problems and empirical results are therefore highly controversial, with several studies reporting relative risk estimates for mortality ranging from neutral to severely harmful. The present study addresses the above problems by using Marginal structural models (Hernàn et al., 2000; van der Laan and Robins, 2003; Bryan et al., 2004).

We review the Belgian National Surveillance Study in Section 4.2 and Marginal structural models in Section 4.3.2. Standard inference for such models cannot be used for estimating the effect of ICU-acquired infection on death for the following reasons. First, these models describe the hazard of death for ICU patients had they acquired infection in the ICU at a given number of days since admission, but this is ill-defined when ICU discharge comes earlier. Second, infection status and confounders were only recorded until ICU discharge, whereas survival times were recorded until hospital discharge to alleviate the problem of informative censoring. Similar difficulties arise in observational studies with a mortality endpoint where exposures are incompletely measured due to loss to follow-up or end-of-study, but survival times are assessed over a much longer time period (e.g. using death registers).

To accommodate both problems, we propose a new class of Marginal structural models in Section 4.3, which express the effect on the hazard of death of acquiring infection on a given day s, versus not acquiring infection up to that day, had patients stayed in the ICU for at least s days. We call such model in our class a Marginal structural proportional hazards model for partial exposure regimes (MSPHM-P), as each considered "exposure regime" specifies the "exposures" (i.e. infections) for a given patient only up to the chosen time point s. This has the added advantage of yielding more stable inferences since we merely aim to infer the effect of avoiding infection during the first s days since admission, and not during the entire ICU stay. It thus makes the new models useful even in settings where standard Marginal structural models can be applied. We derive a class of Consistent and asymptotically normal (CAN) estimators for the parameters indexing our models and provide a reasonably efficient estimator in that class. In Section 4.4, we present results obtained for the surveillance data. In Section 4.5, we discuss the usefulness of MSPHM-Ps in more general settings.

4.2 National ICU surveillance study

All ICUs in Belgian hospitals were invited to participate in this surveillance study on a voluntary basis. For all patients admitted to the ICU, data were recorded on personal characteristics, reasons for ICU admission, baseline health status, and daily indicators of received invasive treatments and acquired infections in the ICU. ICU-acquired infections were defined as infections acquired by patients after the second day of ICU stay, to exclude infections that were in incubation upon enrollment in the ICU. The third day of stay in ICU will thus be the starting point for our analysis, excluding patients who stayed less than 3 days. We will restrict the analysis to surveillance data collected for the year 2002 in one of the largest hospitals which has accurate daily measurements of received invasive treatments and acquired infections. A total of 1072 ICU patients were analysed. Of the 100 (9.3%) patients who acquired ICU-acquired pneumonia in ICU and stayed more than 2 days, 41 (41%) died in hospital, of whom 27 in ICU, as compared to 183 (18.8%) deaths among the 972 patients who remained free of pneumonia in ICU, of whom 99 died in ICU. Among patients who stayed more than 2 days in ICU, the median length of stay in ICU was 4 days (Interquartile range (IQR) 3, 95th percentile 13) for those without a history of ICU and 16 days (IQR 13, 95th percentile 54.5) for the remaining patients.

A preliminary causal analysis (Mertens and Vansteelandt, 2012) using Marginal structural proportional hazards models (MSPHMs) revealed highly unstable results when survival times were censored upon ICU discharge, as a result of high censoring rates. Using patient registers, the survival status of each patient was therefore assessed upon hospital discharge.

4.3 Marginal structural models for partial exposure regimes

4.3.1 Notation

Throughout, we use the following notation. For each patient, let A_t be a counting process that indicates 1 for ICU-acquired pneumonia at or prior to time t and 0 otherwise, where $A_0 = 0$ by definition (see Figure 4.1). Likewise, let D_t (C_t) be a counting process that indicates 1 if ICU (hospital) discharge happened at or prior to time t and 0 otherwise. Define L_0 to be a vector of baseline variables collected upon admission to the ICU. In our analyses, L_0 consists of age, gender, reason for ICU admission, acute coronary care, multiple trauma, presence and type of infections upon ICU admission, prior surgery, baseline antibiotic use and the Simplified acute physiology score II (SAPSII) score, a severity-of-illness score based on a set of 15 clinical parameters predicting the mortality risk of a patient admitted to the ICU (Le Gall et al., 1993). Further, for $t > 0$, define L_t to be a vector of invasive therapeutic treatment indicators collected on day t, consisting of indicators of exposure to mechanical ventilation, central vascular catheter, parenteral feeding, presence and/or feeding through naso- or oro-intestinal tube, tracheotomy intubation, nasal intubation, oral intubation, stoma feeding and surgery. Discharge from the ICU defines the end of follow-up for all measured variables, except survival time, so that A_t and L_t are observed for all t with $D_t = 0$, but not otherwise. Survival time T is censored by discharge from the hospital. We define K to be the end of follow-up time and, for any vector $Z = (Z_0, ..., Z_K)$ and $t \leq K$, $\overline{Z}_t = (Z_0, ..., Z_t)$. Throughout, we assume that infection and discharge on day t can only be affected by time-dependent variables measured on previous days (and thus not by those measured on the same day).

4.3.2 Marginal structural models

Time-dependent multi-state models for event history analysis (Andersen and Keiding, 2002; Schumacher et al., 2007) may appear well-matched to the multi-state

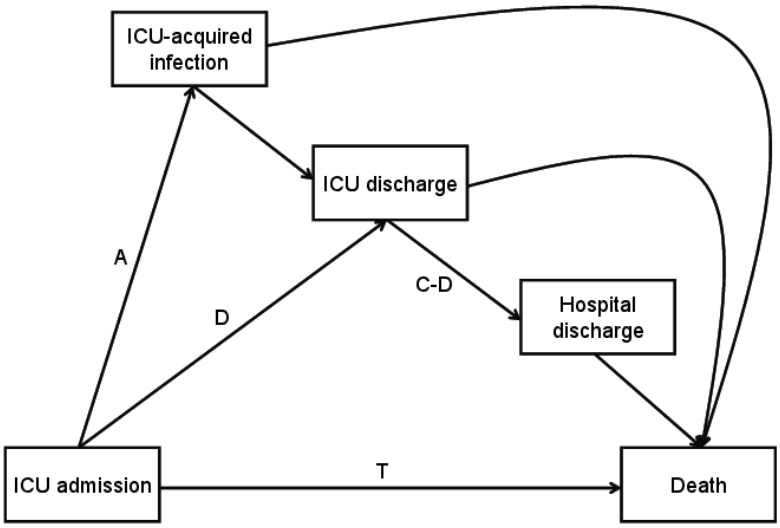


Figure 4.1: Multi-state model: directed arrows show the possible transitions from one state to another.

nature (see Figure 4.1) of our problem. However, they are likely to yield biased estimates of the effect of ICU-acquired infection on mortality, whether or not one adjusts for the relevant past confounder history (Robins, 1997). For the unadjusted analysis, this is so because these analyses ignore time-varying confounders like mechanical ventilation, which increases the risk of infection and is also associated with death. For the adjusted analysis, this is so when these time-varying confounders lie on the causal path from infection to mortality, because standard regression adjustment for such post-infection measurements may introduce bias. This problem of adjusting for internal (or endogenous) time-dependent covariates has long been recognised in the survival literature (see e.g. Andersen (1986) and the discussion in Kalbfleisch and Prentice (2002), but solutions to it have emerged only recently. One such solution, which is becoming increasingly popular among statisticians and epidemiologists, is to use MSPHM (Hernàn et al., 2000). We briefly review these models in this section.

Let $T_{\bar{a}}$ express the counterfactual survival time (Rubin, 1978; Robins, 1986)

which an ICU patient would, possibly contrary to fact, have had under a given infection path $\overline{a} = (a_1, a_2, ..., a_K)$ following which the patient is infected on day t since ICU admission if $a_t = 1$ and uninfected if $a_t = 0$. Then a MSPHM is a proportional hazards regression model for the counterfactual survival time $T_{\overline{a}}$, possibly conditional on baseline covariates V. It thus expresses how the hazard of death would have been if all ICU patients had followed infection path $\overline{a}$. A simple example is

$$\lambda_{\overline{a}}(t|V) = \lambda_0(t) \exp\left(\beta_1 a_t + \beta_2' V\right) \tag{4.1}$$

where $\lambda_{\overline{a}}(t|V)$ is the hazard function that characterises the conditional survival function of $T_{\overline{a}}$, given V. It thus represents the hazard of death at time t among patients with baseline covariates V, had they all followed infection path $\overline{a}$. Further, $\lambda_0(t)$ is an unknown baseline hazard of death at time t and β_1, β_2 are unknown parameters. In model (4.1), $\exp(\beta_1)$ expresses the causal rate ratio at time t due to acquiring infection at time t. This represents the ratio of the mortality rate at any time t had all patients with baseline covariates V acquired infection at time t compared to the mortality rate at time t had these patients acquired no infection up to time t. Further, $\lambda_0(t)$ expresses the hazard of death at time t for patients with $V = 0$ had they followed an infection path in which they never acquired infection in ICU. The model's name "marginal" expresses that the model does not involve time-dependent confounders. Adjustment for such confounders happens by fitting the model to data from a pseudo-population in which there are no time-varying confounders, but the target effect is the same. This pseudo-population is constructed by reweighting subjects in the risk set at each time t by the reciprocal of the product of the conditional probabilities of the observed infection status at each time before time t, given the history of time-varying confounders at that time [see expression (4.5) below] (Hernàn et al., 2000).

The considered MSPHM is not directly applicable in our study because the exposure "ICU-acquired infection" (and, likewise, $T_{\overline{a}}$) is ill-defined between ICU discharge and death or censoring of the survival time. Since our goal is to estimate the effect of "ICU-acquired" infection on mortality, it may seem natural to define patients as uninfected when they were not infected upon ICU discharge. However, this would make standard estimators for marginal structural models

irregular (Robins, 2000) because there would be patients with certain prognostic factors (namely, those who are discharged uninfected from ICU) who are precluded from becoming infected under this definition. This irregularity results from failure of the implicit assumption of experimentation in the "assignment" of infection (van der Laan and Robins, 2003), according to which, at each time $t = 1, ..., K$, it must be true that

$$0 < P(A_t = 1|\overline{A}_{t-1}, \overline{L}_{t-1}, D_t, V) < 1 \text{ with probability 1.}$$

This assumption is needed to avoid inverse weighting by zero [see expression (4.5) below].

Alternatively, one could consider the infection and ICU discharge status of a patient as a joint exposure. Specifically, one could redefine an infection path to be any path (d, a, as) in which a patient, while alive, will be discharged from the ICU on day d and either acquire infection on a given earlier day $s < d$ (if $a = 1$) or stay uninfected during his/her stay in the ICU (if $a = 0$). The joint causal effect of discharge and infection in the ICU on the hazard of death can be expressed as a function of baseline covariates V through MSPHMs for multiple interventions (Hernàn et al., 2001; Robins et al., 2003). The following is a simple example of such a model:

$$\begin{aligned} \lambda_{(d,a,as)}(t|V) &= \lambda_0(t) \exp[\{\beta_1 + \beta_2(t-s)\}aI(t \geq s) \\ &\quad +\{\beta_3 + \beta_4(t-d)\}I(t \geq d) + \beta_5' V] \end{aligned} \tag{4.2}$$

with $d > s$. Here, $\lambda_{(d,a,as)}(t|V)$ is the hazard that characterises the conditional survival function of the counterfactual survival time, given V, under infection path (d, a, as), $\lambda_0(t)$ is an unknown baseline hazard of death at time t, and $\beta_1, \beta_2, \beta_3, \beta_4, \beta_5$ are unknown parameters. In particular, $\exp\{\beta_1 + \beta_2(t-s)\}$ is the causal rate ratio at time t due to acquiring infection at time $s, s \leq t, s < d$. This represents the ratio of the mortality rate at any time t had all patients with baseline covariates V acquired infection at time s compared to the mortality rate at time t had these patients experienced the same discharge time, but no infection up to time t. Note that this causal effect parameter has limited relevance from a public

health perspective. First, it expresses the effect of acquiring pneumonia at a given time on mortality in the hypothetical and unrealistic scenario where we would keep the patients in the ICU until some given, later time. Second, by comparing the same group of patients under two possible infection histories, the time of discharge from the ICU being equal, $\exp\{\beta_1 + \beta_2(t-s)\}$ represents only the direct effect of acquiring infection at time s on mortality at time t. As such, it does not capture the indirect effect of infection on death that may arise when infection prolongs the time of stay in the ICU, which may itself affect mortality risk. Furthermore, preliminary analyses (not displayed) showed that estimates for the parameters in the above model are highly unstable as a result of inverse weighting by small probabilities in the estimation procedure. This is due to a lengthy follow-up for a limited number of patients and because many time-dependent variables are strongly predictive for ICU discharge.

4.3.3 Marginal structural models for partial infection paths

To accommodate the foregoing problems, we will infer mortality rates under infection paths (s, a) in which patients stay in the ICU for *at least* s days and acquire infection (if $a = 1$) or not (if $a = 0$) on day s. Thus, under path $(s, a) = (s, 0)$, patients are uninfected in the ICU up to day s, their infection status being unspecified thereafter; under path $(s, a) = (s, 1)$, patients are uninfected in the ICU up to day s and acquire infection on day s. By analysing mortality rates of ICU patients under each such infection path, we will be able to answer causal questions like "What would be the effect on the mortality rate of ICU patients of acquiring infection at time s, versus not acquiring infection up to that time, had they stayed in the ICU for at least s days?". At the same time, we will be solving the problem that the infection status is unknown or ill-defined after ICU discharge because we only consider infection paths which specify the infection status of patients during their stay in the ICU. As such, these infection paths generalise the deterministic treatment regimes of Robins (1997) which specify the treatment at each time from start until end of study.

For a given path (s, a), let $T_{(s,a)}$ be the random variable representing the sub-

ject's time from admission in the ICU to death had they experienced infection path (s, a) rather than their own infection history, all other things being equal. We can then express the causal effect of infection in the ICU on the hazard of death through MSPHM:

$$\lambda_{(s,a)}(t|V) = \lambda_0(t) \exp\left\{\beta_1 \min(t, s) + \beta_2 a I(t \geq s) + \beta_3' V\right\}. \tag{4.3}$$

Here, $\lambda_{(s,a)}(t|V)$ is the hazard that characterises the conditional survival function, given V, of the counterfactual survival time under infection path (s, a), $\lambda_0(t)$ is an unknown baseline hazard of death at time t, and $\beta_1, \beta_2, \beta_3$ are unknown parameters. Note that $\lambda_0(t) = \lambda_{(0,0)}(t|0)$ is the hazard of death at time t among patients with $V = 0$ and is hence directly identifiable from the observed data distribution. In addition, note that $\exp(\beta_2)$ is the causal rate ratio at time t of acquiring infection at any time $s, s \leq t$. It represents the ratio of the mortality (hazard) rate at any time t had all patients with baseline covariates V stayed in the ICU up to at least time s and acquired infection at that time compared to the mortality (hazard) rate at time t had these patients also stayed in the ICU up to at least time s but acquired no infection up to that time. By specifying only whether infection comes before discharge, $\exp(\beta_2)$ represents the overall effect of acquiring infection at time s on mortality at time t under model (4.3). We call (4.3) a Marginal structural proportional hazards model for partial exposure regimes (MSPHM-P) to express that it determines each exposure regime (i.e. each infection path) only for a limited time period, contrary to the more standard MSPHMs of Section 4.3.2.

4.3.4 Inference

In this section, we develop inference for the parameters indexing MSPHM-Ps under Sequential randomisation assumption (SRA). Specifically, we assume that at each time $t \leq s$, survivors with prognostic factors $\bar{L}_{t-1}, \bar{A}_{t-1}, D_{t-1} = 0$ and V have the same hazard of infection and ICU discharge at time t regardless of their counterfactual survival time $T_{(s,a)}$, for each infection path (s, a) that is compatible with the observed history $(\bar{A}_{t-1}, D_{t-1} = 0)$. That is, for each such path (s, a) and

each $t \leq s$,

$$(A_t, D_t) \amalg T_{(s,a)} | \bar{L}_{t-1}, \bar{A}_{t-1}, D_{t-1} = 0, T > t,$$

where $U \amalg V|W$ for random variables U, V, W indicates that U is conditionally independent of V, given W. This assumption is reasonable when the physician's decision to discharge a patient from the ICU at time t is based solely on daily patient characteristics which were recorded in $\bar{L}_{t-1}, \bar{A}_{t-1}$ and V and, in addition, all time-dependent confounders for the association between infection and death are accounted for.

Even if all patients were observed until the study end or death, analysis tools for MSPHMs (Hernàn et al., 2000) would not be directly applicable to fit model (4.3) under these assumptions because each infection path is specified for only a limited period of time. Below, we give a practical algorithm for obtaining a Consistent and asymptotically normal (CAN) estimator for the parameter $\beta = (\beta_1, \beta_2, \beta_3)'$ indexing model (4.3) in the absence of unmeasured time-dependent confounders. The motivation for this algorithm is given in the Appendix (Section 4.6), where the resulting estimate is defined via weighted partial likelihood estimation.

First we identify, for each infection path (s, a), those patients whose observed infection history is compatible with the path (s, a). For each time t, we thus construct a vector of variables (S_t, A_t^*) which takes the value (s, a) for a given patient at that time if that patient's observed infection path up to time t could have been obtained under the path (s, a). That is, for given s, $(S_t, A_t^*) = (s, 1)$ [or $(S_t, A_t^*) = (s, 0)$] for a given patient at time t if that patient was in the ICU at time $s \leq t$ and acquired pneumonia at that time (or did not acquire pneumonia up to and including that time). In contrast to inference for ordinary MSPHMs, the data for a given patient at a given time may be compatible with multiple infection paths and may thus carry information about more than one path. This is because the considered paths are only partially specified. For instance, if a patient's data are compatible with infection path $(s, 0)$ at time t, then they are compatible with all infection paths $(u, 0)$ for $u < s$, and may thus appear multiple times in the database corresponding to different values of S_t.

Next, for all infection paths (s, a) jointly, we fit a proportional hazards model

using only the data compatible with the given path and weighting each observation by the reciprocal probability of following that path to account for the selective nature of our subsample. Specifically, we substitute (s, a) by (S_t, A_t^*) in the marginal structural model (4.3) by fitting the time-dependent proportional hazards model

$$\lambda(t|S_t, A_t^*, V) = \lambda_0^*(t) \exp\left\{\beta_1^* \min(t, S_t) + \beta_2^* A_t^* + \beta_3^{*\prime} V\right\}, \tag{4.4}$$

and weight the contribution of a patient to the risk set at time t by the stabilised weights

$$\begin{aligned} swi(t, S_t, \bar{A}_t, \bar{D}_t, \bar{L}_{t-1}, V) \;=\; & \prod_{k=1}^{S_t} \frac{P\left(A_k|A_{k-1} = D_k = 0, V\right)}{P\left(A_k|A_{k-1} = D_k = 0, \bar{L}_{k-1}, V\right)} \\ & \times \frac{P\left(D_k = 0|A_{k-1} = D_{k-1} = 0, V\right)}{P\left(D_k = 0|A_{k-1} = D_{k-1} = 0, \bar{L}_{k-1}, V\right)}. \end{aligned} \tag{4.5}$$

These weights differ from the usual stabilised weights for Marginal structural models (Hernàn et al., 2000, 2001) in that they consider the joint treatment process given by infection and discharge at each time and do this only up to the artificial time S_t. Note that they involve the discharge process to account for the fact that, at each time t, those subjects who are still in the ICU (i.e. those for whom we have information on the infection history) may form a selective subset of the study population. The impact of weighting is to eliminate time-varying confounders by removing their association with exposure (A_t, D_t) at each time t, while leaving the causal effect of interest unchanged. The numerator probabilities in (4.5) are included for stabilisation of the weights and are allowed to be misspecified by the fact that model (4.3) is postulated conditional on V.

To deal with censoring of the survival status due to hospital discharge, we proceed under the additional assumption of Ignorable censoring assumption (ICA) (van der Laan and Robins, 2003). For our data and study setting, this assumption states that among subjects with a given observed past $\bar{A}_{t_D}, \bar{D}_t, \bar{L}_{t_{D-}}, V$, where $t_D = \min(t, D-1)$ and $t_{D-} = \min(t, D) - 1$, the censored and uncensored subjects at time t have the same survival time distribution; that is, $C \amalg T|\bar{A}_{t_D}, \bar{D}_t, \bar{L}_{t_{D-}}, V, T > t, C > t$ for each time t. At a given time t, this

assumption could be reasonable for short-term survival rates because we have available a large and detailed collection of prognostic factors for survival that also predict time of discharge from the ICU. However, for given t, it is questionable for the longer term because we lack data monitoring the health status of patients after leaving the ICU. In our study, the median length of stay in hospital after ICU discharge was 8 days (IQR 10, 5% percentile 0, 95% percentile 50).

We can correct the above analysis for ICA by further weighting each patient's contribution to the risk set at time t by the stabilised weights

$$swc(t, \bar{A}_{t_D}, \bar{D}_t, \bar{C}_{t-1}, \bar{L}_{t_D}) = \prod_{k=1}^{t} \frac{P\left(C_k = 0 | \bar{A}_{k_D}, \bar{D}_k, C_{k-1} = 0, V\right)}{P\left(C_k = 0 | \bar{A}_{k_D}, \bar{D}_k, C_{k-1} = 0, \bar{L}_{k_{D-}}, V\right)} \quad (4.6)$$

where the numerator and denominator probabilities equal 1 when $D_k = 0$. Here, we implicitly assume that hospital discharge does not causally affect survival. Under this assumption and provided that the measured time-dependent covariates are sufficient to adjust for time-dependent confounding and censoring due to hospital discharge, fitting model (4.4) and weighting each patient's contribution to the risk set at time t by the product of (4.5) and (4.6) produces a consistent estimator for the causal rate ratio.

4.4 Data analysis

We first consider the unadjusted time-dependent proportional hazards model

$$\lambda(t|\overline{A}_t) = \lambda_0(t) \exp\left(\beta_1 A_t\right)$$

To enhance comparability with later results, we fitted this model via unweighted pooled logistic regression with regression splines for the time effect. The estimate of the hazard ratio of death comparing patients who acquired infection prior to time t and those who did not, was 1.89 [95% Confidence interval (CI) 1.32, 2.71]. When adding baseline covariates (SAPSII score and reasons for admission to the ICU), the estimated hazard ratio was no longer significant and equaled 1.37 (95%

CI 0.93, 2.04).

To adjust for time-dependent confounding, we extended our data set to include S_t and A_t^* for each patient at each time t. Next, we calculated stabilised weights by means of 6 pooled logistic regression models for the numerator and denominator weights in (4.5) and (4.6). To avoid unstable weights, we included baseline covariates (V) in the numerator weights and then later also in the MSPHM-P. Specifically, we considered type of admission allowing for effect modification by acute coronary care and by multiple trauma, presence and type of infection and of surgery at admission, SAPSII score and age (allowing for quadratic effects on both), gender, antibiotic use during the first 48 hours of ICU stay, and baseline values for all previously listed invasive therapeutic treatment indicators. Time-dependent information on exposure to invasive treatments was summarised in terms of the presence/absence of the treatment on each of the 2 previous days and by the total number of previous days on invasive treatments. In addition, we allowed for quadratic effects of the number of previous days on mechanical ventilation additionally allowing for effect modification by antibiotic use during the first 48 hours of ICU stay, and on central vascular catheter. To build parsimonious models, we used the following conservative approach. In the first stage, all main effects were added and then sequentially removed if non-significant at the 10% level (ignoring correlations between outcomes from the same patient). In the second stage, the suggested interaction terms and quadratic effects were added if significant following the same criterion. Splines were used to model the time effect in all models.

Using the estimated predicted values from these models we calculated the probability of each patient having their observed infection status up to time t, given baseline variables and then also given time-dependent variables $\bar{L}_{t-1}$. We calculated similar estimates for the probability of ICU discharge and hospital discharge, the latter after also adjusting for the infection and ICU discharge history. To avoid unstable weights, we considered only infection paths (s, a) with $3 \leq s \leq 11$. This implies that the estimated effect of infection on the hazard of death pertains only to infection paths where infection is acquired during the first 11 days starting from day 3. Note however that we included all observed person-days in

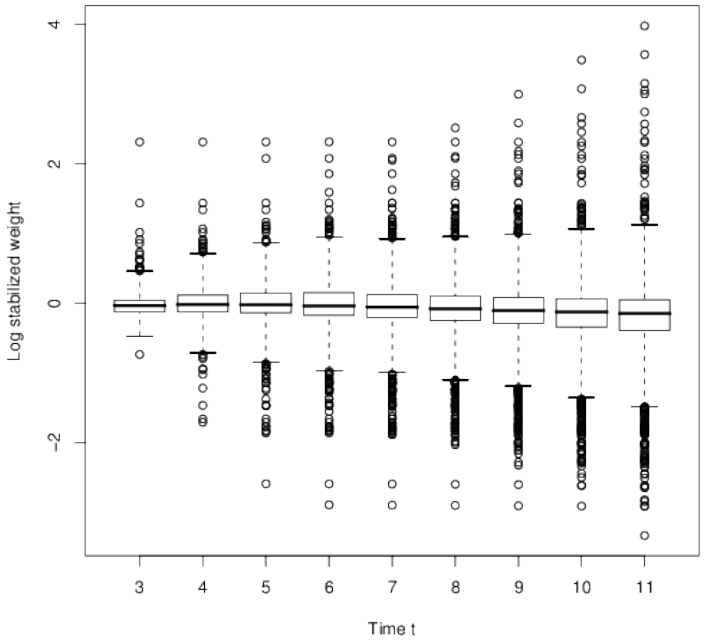


Figure 4.2: Boxplots of the natural logarithm of the stabilised weights in function of time t (with whiskers extending to 2.5 times the interquartile range).

the analysis.

Figure 4.2 displays the distribution of the natural logarithm of the stabilised weights as a function of time. The stabilised weights had a median and mean of 0.81 and 0.93, an interquartile range and standard deviation of 0.48 and 1.94 and 1% and 99% percentiles of 0.048 and 3.89 (min. 0.0039, max. 123.48). Among weights greater than 5, the 99th, 75th and 50th percentiles are 100.59, 11.70 and 8.69. Among weights smaller than 0.2, the 1st, 25th and 50th percentiles are 0.0066, 0.069 and 0.12.

Because standard software for Proportional hazards regression does not allow us to reweight the risk sets at each time, we fit the discrete-time analog of (4.4) via a weighted pooled logistic regression model using Generalised estimating equations (GEE), treating each patient-day as an observation and using regression splines to fit the time effect (Hernàn et al., 2000). Unbiasedness of the estimating equations

under this logistic regression model requires use of the independence working correlation (Vansteelandt, 2007). Note that by using GEE to fit model (4.4) we account for the potentially strong correlation arising in the augmented dataset. This may contain the same observations multiple times corresponding to different values of S_t. Because the effect on the hazard of death at time t of keeping the patient in the ICU up to time S_t was considered a nuisance, we modelled the effect of S_t in model (4.4) using regression splines. Our causal estimate of the hazard ratio for infection was 2.74 [95% conservative CI (1.48, 5.09)]. We conclude that under any infection path in which patients stay in the ICU for at least a given number of days s, the effect of acquiring infection on day s is to multiply the hazard of death by 2.74. Confidence intervals were obtained using the robust standard error. By not taking into account the estimation of the weights, this yields an asymptotically conservative confidence interval for our causal parameters (Robins, 2000). Figure 4.3 shows estimated survival curves for the study population along with 95% confidence intervals, and predicted survival curves in the hypothetical scenario where all patients acquire infection at the third day of their stay in the ICU. It illustrates the severe estimated impact of ICU-acquired infection on mortality.

To examine the stability of the results to extreme weights, we additionally evaluated the effect of infection on mortality for infection paths with $3 \leq s \leq s_{\max} = 7, 8, 9$ and 10. The weights are more stable for these analyses because the product in (4.5) runs over a smaller number of time points. The results are displayed in Table 4.1 and show that the effect size and significance stay the same with increasing stability of the weights. Finally, we performed an ad-hoc procedure whereby stabilised weights smaller than 0.2 or greater than 5 were truncated at 0.2 and 5, respectively. This yielded a hazard ratio of 2.50 [95% conservative CI (1.45, 4.31)], suggesting once more robustness to the extreme weights. Allowing for an interaction between infection status and the number of days since acquiring the infection revealed that, on the hazard scale, the effect of acquiring infection on a given day s increases non-significantly by 2.8% (95% conservative CI (-1.2%, 6.7%), P = 0.17) per day since acquiring infection. Likewise, there was no indication that the effect of ICU-acquired infection on the hazard of death depends on the time at which it was acquired (P = 0.29).

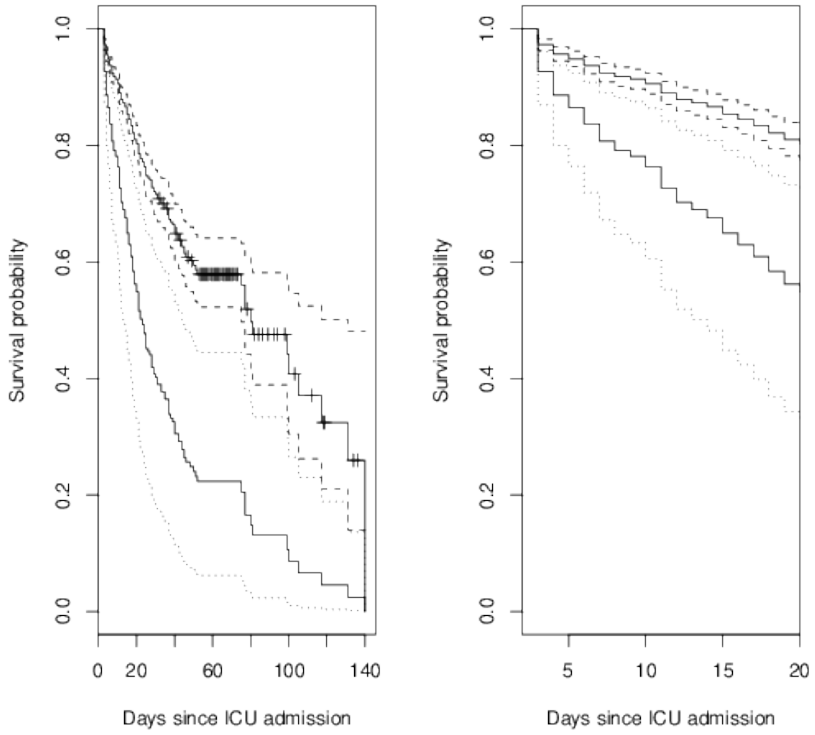


Figure 4.3: Marginal survival curve (upper solid line) (directly estimated from the observed data) with 95% confidence intervals (dashed) and predicted survival curve following immediate infection (lower solid line) (based on the Marginal structural model) with approximate 95% confidence intervals (dotted). The latter intervals acknowledge imprecision on the estimated causal effect, but ignore imprecision on the estimated survival curve. Left: from 3 to 140 days after ICU admission; Right: from 3 to 20 days after ICU admission.

$s_{\max}$	1% perc.	99% perc.	min	max	HR	95% CI
7	0.065	3.50	0.0071	25.94	2.75	(1.48, 5.12)
8	0.064	3.49	0.0061	35.91	2.66	(1.43, 4.94)
9	0.060	3.51	0.0053	54.14	2.70	(1.46, 5.00)
10	0.054	3.72	0.0046	81.88	2.71	(1.47, 5.01)
11	0.048	3.89	0.0039	123.48	2.74	(1.48, 5.09)

Table 4.1: Distribution of the stabilised weights (1% and 99% percentiles, minimum and maximum), glsplhr and 95% confidence intervals in Marginal structural models for partial infection paths with $3 \leq s \leq s_{\max}$.

4.5 Discussion

The effect on mortality of acquiring pneumonia in ICU continues to raise controversy among clinicians because standard statistical analyses have shown contradictory results. Because this is partly due to inappropriate adjustment for intermediate time-varying confounders, we have proposed to use analyses of marginal structural models. These take into account the time order in which infection, mortality data and time-dependent confounders were collected and correct appropriately for time-dependent confounders that lie on the causal path from pneumonia to mortality. Inference for such models was however not directly applicable to our data for the following two reasons: (a) the infection status of patients was ill-defined subsequent to ICU discharge, an event which lies on the causal path from infection to mortality; (b) the usual weights in the weighted estimating equations for standard MSPHMs were highly unstable because there was a lengthy follow-up for several patients and because many collected time-dependent variables were strongly predictive of ICU discharge.

To accommodate these problems we have proposed to model mortality rates under "partially specified" infection paths. The resulting models solve the problem mentioned in (a) without fixing the discharge time after the event of infection and thus without fixing variables on the causal path from infection to mortality. In addition, inference under these models tends to be more stable because each infection path is specified only up to a given time s (rather than up to the study end). As such, the weights in the inverse weighting procedure merely involve the

first s time points and are thus less affected by lengthy follow-up with frequent infection measurements. Alternatively, weight instability may be intercepted by inferring only the effect of late infections, along the lines of Joffe et al. (2004); Petersen et al. (2007), or by using doubly-robust estimators which allow better for truncating extreme weights (Yu and van der Laan, 2006). Finally, note that our results directly accommodate situations where exposures are not collected up to the time where outcomes are assessed. This may happen in settings where the mortality status of patients is assessed at the time of data analysis, i.e. later than end-of-follow-up, through death registers, or where each patient's treatment or treatment compliance is closely monitored for only a limited time period. By not fixing treatment levels observed after this time period, the proposed models isolate the overall effect of treatment over the given period on outcome and extrapolate much less from the observed data than standard MSPHMs.

Alternatively, we could have chosen to assess the effect of avoiding infection among patients who acquired infection on a given day. This effect estimand has greater relevance since physicians are primarily interested in the effect of *preventing* infection among the infected. Also, by restricting the focus to those who acquired infection in the ICU, one avoids the difficulty that the effect of acquiring infection on a given day in ICU is ill-defined for those who get discharged before that day. Structural nested accelerated failure time models (SNFTMs) (Robins, 1992, 1997; Keiding et al., 1999) can be used for modelling this effect estimand. These are models for the effect of a change in infection status on survival time among patients with a given history of measured time-dependent confounders and infection. Because inference for these models is more complicated, does not allow the use of standard software, and typically suffers more from censoring of the survival time, we have chosen to adopt marginal structural models in this article and plan to report on structural nested models elsewhere.

Finally, it remains to be seen how sensitive conclusions are to the untestable assumptions that there are no unmeasured time-varying confounders for the effect of infection on mortality (SRA) and that censoring is sequentially ignorable (ICA). The former assumption implies that among patients with prognostic factors $\bar{L}_{t-1}, \bar{A}_{t-1}, D_{t-1} = 0$, the causal effect of infection and ICU discharge is the same

regardless of their infection and ICU discharge status at time t. This may not be entirely realistic because we anticipate the causal effect of infection to be greater among the infected and we may lack sufficient prognostic factors conditional on which this is no longer so. ICA may also be questioned because the decision to discharge patients from hospital is intimately connected with their health status, about which no information was recorded after ICU discharge. In future work, we plan to accommodate this by estimating the effect of acquiring infection in ICU on "30-day ICU mortality". This endpoint is uncensored and of even greater interest to clinicians, because time to death in ICU patients can be greatly extended by invasive therapeutic treatments.

4.6 Appendix

We will first clarify the relation between the infection paths (d, a, as) and (s, a). Note that the infection path $(d, a, as), (s < d)$ is defined by the infection path $\overline{a} = (a_1, ..., a_{s-1}, a_s, ..., a_K) = (0, ..., 0, a, ..., a)$ following which a patient is infected on a given day t since ICU admission if $a_t = 1$ and uninfected if $a_t = 0$, and additionally by the discharge path $\overline{d} = (d_1, ..., d_{d-1}, d_d, ..., d_K) = (0, ..., 0, 1, ..., 1)$ following which a patient is in the ICU on a given day t since ICU admission if $d_t = 0$ and has been discharged if $d_t = 1$. The infection path (s, a) is defined by the same infection path, but a discharge path $\overline{d} = (d_1, ..., d_{s-1}, d_s, ..., d_K) = (0, ..., 0, D_s, ..., D_K)$ which is only partially specified.

In the remainder of this Section, we will construct a class of unbiased estimating functions for the parameters indexing MSPHM-Ps which contains (up to asymptotic equivalence) all such unbiased estimating functions. For each patient in the study, let D be the observed time from admission in the ICU to discharge from ICU. Note that D can be recovered from the path $\{D_t, t = 0, ..., K\}$ (up to the resolution permitted by discrete time). Let us first assume there is no censoring due to hospital discharge. Then we develop inference for β indexing model $\mathcal{M}$ for the observed data $\left(T, D, \bar{A}_{D-1}, \bar{L}_{D-1}\right)$ defined by the law of the infection and discharge process under SRA (i.e. the assumption of no unmeasured confounding for infection and

ICU discharge):

$$f(D_D = 1|\bar{A}_{D-1}, \bar{D}_{D-1} = 0, \bar{L}_{D-1}, V) \\ \times \prod_{t=1}^{D-1} f(A_t, D_t = 0|\bar{A}_{t-1}, \bar{D}_{t-1} = 0, \bar{L}_{t-1}, V) \tag{4.7}$$

where f is an unknown probability function, and by a discrete-time marginal multiplicative intensity model (Fahrmeir and Tutz, 1994), e.g.:

$$\lambda_{(s,a)}(t|V) = \lambda_0(t) \exp(\beta' W) \tag{4.8}$$

for $t = 0, 1, 2, ...$, $a = 0, 1$, $s = 1, ..., K$ for a given integer constant $K > 0$, where $W = W(a, s, t, V)$ is a known function of a, s, t and V. Note that model (4.3) in the article is a special case of (4.8) with $\beta = (\beta_1, \beta_2, \beta_3)'$ and $W(a, s, t, V) = \{sI(t \geq s), aI(t \geq s), V\}$. When the hazard $\lambda_{(s,a)}(t|V)$ is small at each time t, this model can be approximated via the discrete-time marginal logistic regression model:

$$\log\left\{\frac{\lambda_{(s,a)}(t|V)}{1 - \lambda_{(s,a)}(t|V)}\right\} = \log\{\lambda_0^*(t)\} + \beta' W \tag{4.9}$$

with regression splines to fit $\log\{\lambda_0^*(t)\}$, as used in the data analysis.

To determine an unbiased estimating function U under model $\mathcal{M}$, let $U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}$ be an unbiased estimating function for β in the full data model defined by the full data $\{T_{(s,a)}, V\}$, restriction (4.8) just for the given t and the given infection path (s, a). Because (4.8) is a discrete-time multiplicative intensity model, such estimating functions follow from standard results on such models. In particular, it may be the discrete-time partial likelihood score, which for a given subject equals

$$\left[W(s, a, t, V) - \frac{\sum_{i=1}^n W(s, a, t, V_i) I\{T_{i,(s,a)} \geq t\} \exp\{\beta' W(s, a, t, V_i)\}}{\sum_{i=1}^n I\{T_{i,(s,a)} \geq t\} \exp\{\beta' W(s, a, t, V_i)\}}\right] dN(t) \tag{4.10}$$

where $T_{i,(s,a)}$ is the realisation of $T_{(s,a)}$ for the ith subject and where $dN(t)$ indicates 1 if the counterfactual survival time $T_{(s,a)} \in]t-1, t]$ for the considered subject. In the data analysis, $U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}$ is the score function for β in the logistic regression model (4.9).

Define

$$U = \sum_{t=1}^{K} \sum_{s=1}^{t-1} \sum_{a=0}^{1} I(A_s = a, A_{s-1} = 0, D_s = 0) sw_{s,a}(\overline{L}_{s-1}) U_{t,(s,a)}\{T_{(s,a)}, V; \beta\} \tag{4.11}$$

with

$$\begin{aligned} sw_{s,a}(\overline{L}_{s-1}) &= \frac{P(A_s = a, D_s = 0 | A_{s-1} = D_{s-1} = 0, V)}{P(A_s = a, D_s = 0 | A_{s-1} = D_{s-1} = 0, \bar{L}_{s-1}, V)} \\ &\quad \times \prod_{k=1}^{s-1} \frac{P(A_k = D_k = 0 | A_{k-1} = D_{k-1} = 0, V)}{P(A_k = D_k = 0 | A_{k-1} = D_{k-1} = 0, \bar{L}_{k-1}, V)} \end{aligned} \tag{4.12}$$

Then U is an unbiased estimating function in model $\mathcal{M}$. Indeed, first note that U is a function of the observed data because replacing $T_{(s,a)}$ by T yields the same full data function under the Consistency assumption that we observe $T_{(s,a)} = T$ for subjects with $A_s = a, A_{s-1} = 0, D_s = 0$. Furthermore, for $s < t - 1$ and provided that SRA holds,

$$\begin{aligned} & E\left[I(A_s = a, A_{s-1} = 0, D_s = 0) sw_{s,a}(\overline{L}_{s-1}) U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}\right] \\ = \; & E\left[E\{I(A_s = a, D_s = 0) sw_{s,a}(\overline{L}_{s-1}) | A_{s-1} = D_{s-1} = 0, \bar{L}_{s-1}, T_{(s,a)}\}\right. \\ & \left. \times I(A_{s-1} = D_{s-1} = 0) U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}\right] \\ = \; & E\left[E\{I(A_s = a, D_s = 0) sw_{s,a}(\overline{L}_{s-1}) | A_{s-1} = D_{s-1} = 0, \bar{L}_{s-1}\}\right. \\ & \left. \times I(A_{s-1} = D_{s-1} = 0) U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}\right] \\ = \; & E\left[P(A_s = a, D_s = 0 | A_{s-1} = D_{s-1} = 0, V)\right. \\ & \left. \times I(A_{s-1} = D_{s-1} = 0) sw_{s-1,0}(\overline{L}_{s-2}) U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}\right] \\ = \; & \ldots \\ = \; & E\left[U_{t,(s,a)}\{T_{(s,a)}, V; \beta\} P(A_s = a, D_s = 0 | A_{s-1} = D_{s-1} = 0, V)\right. \\ & \left. \times \prod_{k=1}^{s-1} P(A_k = D_k = 0 | A_{k-1} = D_{k-1} = 0, V)\right] = 0 \end{aligned} \tag{4.13}$$

where the last equality is true because the estimating functions $U_{t,(s,a)}\{T_{(s,a)}, V; \beta\}$ are conditionally unbiased given V. We conclude that U is an unbiased estimating function.

Note that the estimating functions used in the article were obtained this way. For instance, solving an estimating equation with estimating function U and $U_{t,(s,a)}\left(T_{(s,a)}, V; \beta\right)$ as given in (4.10) is mathematically equivalent to fitting the time-dependent, discrete-time multiplicative intensity model

$$\lambda(t|V) = \lambda_0(t) \exp\left\{\beta' W(A_t^*, S_t, t, V)\right\}, \tag{4.14}$$

where $\lambda_0(t)$ is an unknown baseline hazard, where $A_t^*, S_t, t > 0$ are defined as in Section 3.4, and where the risk set at each time is weighted by the weights (4.12). Note that (4.14) and (4.12) are obtained by substituting (s, a) by (S_t, A_t^*) in the multiplicative intensity model (4.8) and the weights $sw_{s,a}(\overline{L}_{s-1})$, respectively. Similarly, as in the data analysis, the discrete-time marginal logistic regression model (4.9) can be fitted upon substituting (s, a) by (S_t, A_t^*) and weighting the corresponding subject's contribution at time t by $sw_{S_t,A_t^*}(\overline{L}_{S_t-1})$.

Starting from the single unbiased estimating function for β in model $\mathcal{M}$ that we have now identified, we will construct a class of unbiased estimating functions for β in model $\mathcal{M}$ which contains (up to asymptotic equivalence) all such unbiased estimating functions. Upon noting that SRA is equivalent to ICA, even when the length D of the infection period is random, this construction follows from standard results on the construction of CAN estimators for parameters indexing a conditional mean model under ICA (Robins et al., 1999). Indeed, application of Theorem 1.3 in van der Laan and Robins (2003) shows that, up to asymptotic equivalence, all CAN estimators of β under model $\mathcal{M}$ can be obtained by solving an estimating equation based on estimating functions in the set $\{U\} + T_{SRA}$, where U is an arbitrary unbiased estimating function for β under this model (as already constructed) and where T_{SRA} is the tangent space (Bickel et al., 1993) for the infinite-dimensional parameters indexing the infection and discharge process (4.7), which is assumed to satisfy SRA. A similar argument as in Theorem 1.2 (van der Laan and Robins, 2003) shows that $T_{SRA} = T_{SRA,1} + T_{SRA,2}$ where

$$\begin{aligned} T_{SRA,1} \quad = \quad & \Bigg[\sum_{s=1}^{D-1} Z_s\left(\bar{A}_s, \bar{D}_s, \bar{L}_{s-1}, V\right) \\ & -E\{Z_s\left(\bar{A}_s, \bar{D}_s, \bar{L}_{s-1}, V\right)|\bar{A}_{s-1}, \bar{D}_{s-1}, \bar{L}_{s-1}, V\} : Z_s \text{ arbitrary}\Bigg] \end{aligned}$$

$$T_{SRA,2} = \big[Z(\bar{A}_{D-1}, \bar{D}_D, \bar{L}_{D-1}, V) - E\{Z(\bar{A}_{D-1}, \bar{D}_D, \bar{L}_{D-1}, V)|\bar{A}_{D-1}, \bar{D}_{D-1}, \bar{L}_{D-1}, V\} : Z \text{ arbitrary}\big] \tag{4.15}$$

It further follows from Theorem 1.2 in van der Laan and Robins (2003) that for given estimating function U, the choices $Z_s\left(\bar{A}_s, \bar{D}_s, \bar{L}_{s-1}, V\right) = E\left(U|\bar{A}_s, \bar{D}_s, \bar{L}_{s-1}, V\right)$ and $Z\left(\bar{A}_D, \bar{D}_{D+1}, \bar{L}_D, V\right) = E\left(U|\bar{A}_D, \bar{D}_{D+1}, \bar{L}_D, V\right)$ are optimal in the sense that they yield an efficient estimator of β under model $\mathcal{M}$ in the class of estimators obtained by solving estimating equations in the class $\{U\} + T_{SRA}$ for given U.

Finally, the above methods are easily adapted to handle ICA following the lines of van der Laan and Robins (2003) and to account for estimation of the parameters indexing the infection and discharge process (4.7). It also follows from Theorem 2.4 in van der Laan and Robins (2003) that we obtain an asymptotically conservative confidence interval for our causal parameters by not taking into account estimation of the weights, provided that the unknown parameters in the models for the weights are efficiently estimated.

CHAPTER 5

Augmented and doubly-robust G-estimation under Structural nested accelerated failure time models

This chapter is based on an article currently being prepared for submission, and which is written in collaboration with S. Vansteelandt.

Summary

Structural nested failure time models (SNFTMs) are models for the effect of a time-dependent exposure on a survival outcome. They have been introduced along with so-called G-estimation methods to provide valid adjustment for time-dependent confounding induced by time-varying variables. Adjustment for informative censoring in SNFTms is possible via inverse probability of censoring weighting (IPCW). In the presence of considerable dropout, this can imply substantial information loss and consequently imprecise effect estimates. In this article, we aim to increase the efficiency of IPCW G-estimators under a SNFTM by deriving an augmented estimator that uses both censored and uncensored observations, and offers robustness against misspecification of the model for the censoring process, provided that a

model for a specific functional of the survival time and time-dependent covariates is correctly specified. The empirical properties of the proposed estimators are studied in a simulation experiment, and the estimators are used in the analysis of surveillance data from the field of hospital epidemiology.

5.1 Introduction

Structural nested accelerated failure time models (SNFTMs) (Robins, 1992, 1998)) are models for the effect of a time-dependent exposure variable on a survival outcome. G-estimation under such models can successfully adjust for time-dependent confounding by time-varying variables satisfying the following three conditions: being predictive for (i) outcome, (ii) exposure, and (iii) affected by previous exposure (Robins, 1986). In particular, under the usual assumptions of correct model specification and of no unmeasured confounding, G-estimation for SNFTMs yields estimates for the causal effect of the considered time-dependent exposure variables on the survival outcome on a relative risk scale. This is in contrast to standard methods, for example Cox proportional hazards regression with time-dependent predictors, which will typically yield biased estimates of the joint exposure effect on the hazard of survival whether or not one adjusts for aforementioned time-varying variables (Robins, 1992).

In the presence of censored survival times, G-estimation procedures can be adjusted to prevent selection bias due to censoring or dropout being possibly correlated with survival. This is possible using Inverse probability of censoring (IPC) weights under the Ignorable censoring assumption (ICA) (Robins, 1998). Using this procedure, the estimating equations that define the G-estimator for each subject are weighted by the reciprocal of the cumulative probability of not being censored throughout follow-up, and this using IPC weights that are derived from subjects with observed and censored survival times. However, because the G-estimation procedure relies only on subjects who have an observed survival time, this analysis gives inefficient estimates especially in datasets with high rates of censoring. Moreover, when particular covariates are strongly associated

with censoring (which leads to highly variable IPC weights), using the Inverse probability of censoring weighted (IPCW) G-estimator will necessitate to make a tradeoff between the bias due to incorporating subjects with extreme weights, and the possibility of bias due to truncating these extreme weights towards less influential values. Furthering ideas by Robins (2000), van der Laan and Robins (2003) and Tsiatis (2006), we address these issues by proposing an Augmented Inverse probability of censoring weighted (A-IPCW) G-estimator that is more efficient and also doubly-robust in the sense that it protects against misspecification of either the model for the censoring event or a model for a functional of the survival time and time-dependent covariates, but not necessarily both.

The above introduced methods will be used for the estimation of the attributable effect on mortality of Healthcare-associated infection (HAI). We will use a SNFTM to verify what would happen with the distribution of survival times of hospitalised patients under a hypothetical intervention that would eliminate these infections.

This article is structured as follows. After a brief description of notation in section 5.2, section 5.3 summarises concepts on SNFTMs, G-estimation of their causal parameters, and correction for (non-)administrative censoring. Section 5.4 introduces the augmented estimator that offers doubly-robustness against misspecification of the models for the drop-out process or the outcome. Sections 5.5 and 5.6 show a simulation experiment and an application, and are followed by a discussion. The Appendix gives technical details on the derivation of the augmented estimator and its robustness properties, explains the implementation of estimation routines into statistical software, and gives further details on the simulation and application.

5.2 Notation, definitions and identifying assumptions

Data is assumed to have derived from a cohort with longitudinal follow-up at discrete time points $t = (0, 1, .., T_m)$, with T_m the fixed maximum follow-up time. The time point t is used to index the following time-varying variables. In this

Chapter, we let variable C_t indicate whether a subject was under follow-up ($C_t = 1$) or was lost from follow-up ($C_t = 0$) at or before time t. Let variable A_t indicate if a subject was exposed ($A_t = 1$) or not ($A_t = 0$) at t. L_t is a multidimensional vector of confounders and effect modifiers. Variable Y_t indicates whether a subject acquired the studied outcome ($Y_t = 1$) or not ($Y_t = 0$) by t, and will only be observed at time points were $C_t = 1$. Variables (A_t, C_t, Y_t) are assumed to have absorbing state at $(1, 0, 1)$. At $t = 0$, we define $A_0 = D_0 = 0, C_0 = 1$, and L_0 as a vector of baseline variables. Let $V_t = (C_{t-1}A_t, C_{t-1}L_t)$ be the set of observed prognostic variables at time t. For any time-dependent variable (or combination thereof) Z_t, let $\overline{Z}_t = (Z_0, Z_1, ..., Z_t)$. We assume the following order of events at each time point: $L_t \rightarrow A_t \rightarrow (C_t, Y_t)$.

Let the survival time T be the discrete time from study start at $t = 0$ until the event of interest $Y_t = 1$. T is only observed for subjects with $Y_t = 1$ during study follow-up. Survival time will be administratively censored at T_m for subjects with $Y_{T_m} = 0$. Let $T_{t,0}$ be the subject's time until the event of interest that would have occurred had he or she experienced the observed exposure history $\overline{A}_{t-1}$ until $t - 1$, but zero exposure from time t onwards (Rubin, 1974; Robins, 1998). This is a counterfactual survival time because it is unobserved for subjects who were exposed. We define the following assumptions under which the distribution of $T_{t,0}$ can be identified. The *Consistency assumption* (Cole and Frangakis, 2009; Vanderweele, 2009) states that the counterfactual survival time $T_{t,0}$ at any $t \leq T$ equals the observed survival time T for subjects who were unexposed through follow-up (ie. with $A_T = 0$). The *Sequential randomisation assumption (SRA)* (Rosenbaum and Rubin, 1983; Robins et al., 1992) $T_{t,0} \amalg A_t | \overline{A}_{t-1}, \overline{L}_t, T \geq t$ states that at each time t the counterfactual exposure-free survival time $T_{t,0}$ is independent of exposure A_t, given the history $\overline{A}_{t-1}, \overline{L}_{t-1}$ of exposure and of measured confounders, among subjects who are alive just prior to time t. For observational data, SRA is also referred to as the "assumption of no unmeasured confounding". It states that adjustment for the observed history $(\overline{A}_{t-1}, \overline{L}_t)$ suffices to identify the causal effect of exposure A_t on survival. The *Ignorable censoring assumption (ICA)* (Robins, 1992; Robins et al., 1994; Rubin, 1976) $T_{t,0} \amalg C_t | \overline{A}_t, \overline{L}_t, C_{t-1} = 1, T_{t,0} \geq t$ for each $t > 0$ states that the observed history $(\overline{A}_t, \overline{L}_t)$ is sufficient to predict censoring at

time t in the sense that censoring carries no residual information about survival, conditional on the covariate history up to time t. Finally, we make the *Positivity* assumption (Rosenbaum and Rubin, 1983) that $P(C_t = 1|C_{t-1} = 1, \overline{A}_t, \overline{L}_t, T \geq t) > 0$ for each $t > 0$ with probability 1.

5.3 Estimation of causal parameters under SNFTMs

5.3.1 Mapping of counterfactual survival times

A Structural accelerated failure time model (SFTM) (Cox and Oakes, 1984) postulates that

$$T_{1,0} \stackrel{d}{=} \sum_{t=1}^{T} \exp\{\gamma(t, \overline{A}_t, \overline{L}_t; \psi_0)\} \tag{5.1}$$

with $\gamma()$ a known function of time, $(\overline{A}_t, \overline{L}_t)$ and an unknown parameter vector ψ_0 of dimension p, satisfying $\gamma() = 0$ if $\psi_0 = 0$ or $A_T = 0$. The "$\stackrel{d}{=}$" stands for equality in distribution. The parameter ψ_0 encodes the causal effect of exposure on survival time because it enables mapping the observed survival time T into the counterfactual survival time $T_{1,0}$ under the absence of exposure. For example, taking $\gamma(\overline{A}_t, \overline{L}_t; \psi_0) = \psi_0 A_t$, then $\psi_0 < 0$, $\psi_0 > 0$ and $\psi_0 = 0$ will indicate a beneficial, harmful and neutral effect of exposure respectively; the SFTM's ψ_0 coefficient then parametrises the causal survival ratio (T/T_0) on the log scale. The causal null hypothesis $H_0 : T \stackrel{d}{=} T_{1,0}$ can be studied by testing $\psi_0 = 0$.

In what follows, we will use the more restrictive SNFTM (Robins, 1992), which models, at each time t, the counterfactual survival time $T_{t,0}$ corresponding to observed exposure history $\overline{A}_{t-1}$ until $t-1$, but zero exposure from time t onwards. In particular, it postulates that for subjects who are alive at time t and have covariate history $(\overline{A}_t, \overline{L}_t)$,

$$T_{t,0} \stackrel{d}{=} t - 1 + \sum_{u=t}^{T} \exp\{\gamma(\overline{A}_u, \overline{L}_u; \psi_0)\} \tag{5.2}$$

Estimating ψ_0 in the the above SNFTM will enable us to answer the question "For

each remaining day under exposure, what would be the change in the remaining time to outcome when removing this exposure?".

5.3.2 The G-estimation procedure

Let $T_{t,0}(\psi)$ be the counterfactual exposure-free survival time generated by SNFTM (5.2), for a given candidate parameter ψ for the true but unknown ψ_0. We assume no censoring of survival time for the moment. The G-estimation procedure introduced by Robins (1992) then proceeds by validating the chosen value ψ by using $T_{t,0}(\psi)$ as a substitute for $T_{t,0}$ and evaluating if it obeys SRA. Under this assumption, counterfactuals are independent of actual exposure status at each time conditionally on the exposure and covariate history. To assess this conditional independence we will construct a model for exposure at each time t. With binary, time-dependent and monotonous exposure, we will model the discrete-time hazard of exposure using a pooled logistic regression model of the form

$$E(A_t|A_{t-1} = Y_{t-1} = 0, \overline{L}_t) = \text{expit}(\alpha_t \overline{L}_t) \tag{5.3}$$

for $t = 1, ..., T_m$, with $E(A_t|A_{t-1} = Y_{t-1} = 0, \overline{L}_t)$ the discrete-time hazard of exposure at time t and $\text{expit}(u) = \exp u/(1 + \exp u)$. The causal G-estimate $\hat{\psi}$ of ψ_0 is then found as the value of ψ that gives an estimate of η equalling 0 in the following pooled logistic regression model

$$E(A_t|\overline{A}_{t-1} = \overline{Y}_{t-1} = \overline{0}_{t-1}, \overline{L}_t) = \text{expit}[\alpha' \overline{L}_t + \eta' g_t\{T_{t,0}(\psi), \overline{L}_t\}] \tag{5.4}$$

for $t = 1, ..., T_m$, with $g_t()$ a known vector function of dimension p. G-estimation may proceed via a grid-search, ie. defining a starting range of ψ values and increment, and then scanning this range until acceptable values are found.

Estimates for ψ_0 can alternatively be obtained by solving an estimating equation $U(\psi) = \sum_i \sum_{t=1}^{T} U_{it}(\psi) = 0$ for ψ, with

$$\begin{aligned} U_{it}(\psi) &= g_t\{T_{i,(t,0)}(\psi), \overline{L}_{it}\}\{A_{it} - E(A_{it}|A_{it-1} = Y_{it-1} = 0, \overline{L}_{it}; \hat{\alpha})\} \\ &\quad \times (1 - A_{it-1})(1 - Y_{it-1}) \end{aligned} \tag{5.5}$$

which is the Score function for the coefficient η in model (5.3). Because under SRA, the hypothesis $\psi = \psi_0$ corresponds to $\eta = 0$ in (5.4), we use predictions of $E(A_t|A_{it-1} = Y_{it-1} = 0, \overline{L}_t; \hat{\alpha})$ under model (5.3), thus not depending on $T_{t-1,0}(\psi)$, in function (5.5). The function $U(\psi) = 0$ can be viewed as an unstandardised score statistic for the null hypothesis $\eta = 0$ in model (5.4). Because $n^{-1/2}U(\psi)$ is asymptotically normally distributed with mean zero and variance given by $\Sigma\{U_i(\psi)\}$, the variance-covariance matrix of $U_i(\psi) = \sum_{t=1}^{T} U_{it}(\psi)$, finding the root of $U(\psi)$ is usually done by minimising the test statistic $S(\psi) = n^{-1}U(\psi)'\Sigma\{U_i(\psi)\}^{-1}U(\psi)$ (Robins, 1992), with the point estimate $\hat{\psi}$ of ψ_0 being the value of ψ that gives $S(\psi) = 0$.

5.3.3 Censoring of survival time

The above SNFTM and G-estimation procedure is only valid when the survival times T of all individuals have been observed. In case of *administrative censoring* however, which happens whenever T surpasses the end-of follow-up time T_m, only $X = \min(T, T_m)$ will be observed. Attention must be given not to use the truncated survival time X to calculate $T_{t,0}(\psi_0)$ from SNFTM (5.2). Indeed, because T_m is independent of exposure (through the definition of administrative censoring), using the observed exposure history until T_m may result in values $T_{t,0}(\psi_0)$ that depend on exposure history, thereby violating SRA with $T_{t,0}(\psi_0)$ in lieu of $T_{t,0}$. To accommodate this, under the one-parameter SNFTM $\gamma(\overline{A}_t, \overline{L}_t; \psi_0) = \psi_0 A_t$, the following derivation is commonly considered when calculating the counterfactual exposure-free administrative censoring time $T_{m(t,0)}(\psi)$ for candidate ψ parameters (Robins, 1992; Joffe et al., 2012):

$$T_{m(t,0)}(\psi) = t - 1 + (T_m - t + 1)\exp\{\psi I(\psi < 0)\} \tag{5.6}$$

and

$$\Delta_{t,0}(\psi) = I\{T_{t,0}(\psi) < T_{m(t,0)}(\psi)\} \tag{5.7}$$

$$X_{t,0}(\psi) = \min\{T_{t,0}(\psi), T_{m(t,0)}(\psi)\} \tag{5.8}$$

with $\Delta_{t,0}(\psi)$ $X_{t,0}(\psi)$ and $X_{t,0}(\psi)$ the re-censored counterfactual outcome indicator and survival time respectively. At each t, $T_{m(t,0)}(\psi)$ is the sum of the passed time t and the remaining counterfactual exposure survival time $(T_m - t)\exp\{\psi I(\psi < 0)\}$ under the "most harmful exposure" history, which is defined as the combination of exposures that provides the biggest contraction of the remaining $T_m - t$ days until end-of-follow-up time T_m. In what follows, we replace $g_t\{T_{t,0}(\psi), \overline{L}_t\}$ with $g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\}$.

Additionally, when subjects drop out before arriving at the end of follow-up time T_m, their corresponding survival times T are unobserved as well, this time due to *non-administrative censoring*. Incorporating data from subjects with non-administrative censoring is particularly worrysome when the reason for drop-out or censoring is linked to the unobserved survival time. Restricting the analysis to cases who did not drop out, ie. had an observed survival time $T \leq T_m$ or who were still under follow-up at T_m, may then induce selection bias in the estimates of ψ_0. Also, because exposure is only defined under follow-up, we append $C_{t-1} = 1$ to the conditioning events of the SRA and of the models for exposure (5.3) and (5.4). Selection bias can be eliminated under ICA by solving the weighted complete-case estimating equation

$$U(\psi) = \sum_i C_{iT} U_i(\psi) = \sum_i \sum_{t=1}^{X} \frac{C_{iT} U_{it}(\psi)}{W_{it}^{\text{stab}}} = 0. \tag{5.9}$$

for ψ, with $U_{it}(\psi)$ now being

$$\begin{aligned} U_{it}(\psi) \;=\; & g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\} \\ & \times\{A_{it} - E(A_{it}|A_{it-1} = Y_{it-1} = 0, C_{it-1} = 1, \overline{L}_{it}; \hat{\alpha})\} \\ & \times(1 - A_{it-1})(1 - Y_{it-1}) \end{aligned} \tag{5.10}$$

and

$$W_{it}^{\text{stab}} = \prod_{s=t}^{X_i} \frac{\pi_s(\overline{V}_{is}; \phi)}{\pi_s(V_{i0}; \phi^*)} \tag{5.11}$$

with

$$\pi_s(\overline{V}_{is}; \phi) = P(C_s = 1|Y_{s-1} = 0, C_{s-1} = 1, \overline{V}_{is}) \tag{5.12}$$

in which $P(C_t = 1|Y_{t-1} = 0, C_{t-1} = 1, \overline{V}_t)$ is the conditional probability of being censored at t conditional on being uncensored until then, modelled by known functional $\pi_t(\overline{V}_t; \phi)$ and unknown parameter vector ϕ. These probabilities can be obtained by discrete-time logistic regression, for example $\pi_t(\overline{V}_t; \phi) = \text{expit}\{\phi'(1, V_t)\}$. We will call the solution to (5.9) the IPCW G-estimator. It only takes into account the complete cases described above (having $C_{iT_m} = 1$), who are inversely weighted by the cumulative conditional probability of remaining uncensored from time t onwards, defined by the product of $\pi_s(\overline{V}_{is}; \phi)$ in (5.12). See Appendix 5.8.1 for a proof of the unbiasedness of estimating function (5.9). The probabilities $\pi_s(V_{i0}; \phi^*)$ are included in the denominator of W_{it}^{stab} to make IPC weights more stable, ie. less variable. They are obtained from a similar model as (5.12).

5.3.4 Choices for $g_t()$

Partial robustness against misspecification of the exposure model can be achieved by defining

$$g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\} \quad = \quad \Delta_{t,0}(\psi) - \exp(\beta' \overline{L}_t) \int_t^{X_{t,0}(\psi)} \lambda_{0,t}(s) ds \quad (5.13)$$

in estimating equation (5.9), with $\lambda_{0,t}(.)$ the unknown baseline hazard function and β the unknown parameter vector obtained under the landmark Cox Regression model

$$\lambda_t(s) = \lambda_{0,t}(s) \exp(\beta' \overline{L}_t), s \geq t \quad (5.14)$$

for the hazard of $X_{t,0}(\psi)$ amongst subjects with $X_{t,0}(\psi) \geq t$. Because $X_{t,0}(\psi)$ and $\Delta_{t,0}(\psi)$ can only be derived for subjects with observed or administratively censored survival time, Cox model (5.14) is fitted using subject-times inversely weighted for earlier derived cumulative censoring probabilities (5.11).

The martingale residual (5.13) (Therneau et al., 1990) contrasts the counterfactual outcome indicator under SNFTM (5.2) with its conditional expectation obtained

under model (5.14). Using such parametrisation for $g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\}$ has the advantage of providing partial robustness against misspecifying the exposure model, because an estimating function with mean zero at the true exposure effect ψ_0 is obtained when either the model for onset of exposure $E(A_t|A_{t-1} = Y_{t-1} = 0, C_{t-1} = 1, \overline{L}_t; \hat{\alpha})$ or the model for the counterfactual hazard of $X_{t,0}(\psi)$ conditional on $(X_{t,0}(\psi) \geq t, \overline{A}_{t-1}, \overline{L}_t)$ is correctly specified, but not necessarily both. Estimators that use (5.13) will be therefore called a Exposure risk doubly-robust (EXPDR) G-estimators. Furthermore, because parametrisation (5.13) delivers a conditional mean-zero choice for $g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\}$, it can be shown that it will improve efficiency of the estimator based on estimating function (5.5), see Vock et al. (2013, appendix B.5) for a proof of this in similar settings.

5

5.4 Augmented G-Estimation of ψ_0

Estimates obtained by estimating function (5.9) are inefficient as they ignore observations from subjects who were non-administratively censored during the study. Robins et al. (1994) and Scharfstein et al. (1999) introduced Augmented Inverse probability of censoring weighted (A-IPCW) estimators specifically to improve the efficiency of IPCW estimators. We apply such augmentation to the IPCW G-estimator that solves (5.9), resulting in the A-IPCW estimating function of the form:

$$C_T U(\psi) + \sum_{t=1}^{T_m} \frac{m_t(\overline{V}_t; \xi)}{\pi_t(\overline{V}_t; \phi)} \{\pi_t(\overline{V}_t; \phi) - C_t\} C_{t-1} \tag{5.15}$$

with $C_T U(\psi)$ defined as in (5.9) and

$$m_t(\overline{V}_t; \xi) = E\left\{C_{T_m} U(\psi) | \overline{V}_t, C_{t-1} = 1\right\} \tag{5.16}$$

a model for the full data estimating function $U(\psi)$, represented by known function $m_t()$ and unknown parameter vector ξ, for instance a linear model such as $m_t(\overline{V}_t; \xi) = \xi'(1, \overline{V}_t)$.

Equation (5.15) is derived from IPCW estimating function (5.9) with the objective of obtaining an efficient estimator for ψ_0 within the class of estimators obtained by augmenting the corresponding IPCW G-estimator with unbiased estimating functions under the models for the censoring mechanism $\pi_t(\overline{V}_t;\phi)$ (5.12), and provided that the full data model (5.16) is correctly specified. For this derivation, we relied on semiparametric theory concepts described elsewhere (van der Laan and Robins, 2003; Tsiatis, 2006), see Appendix 5.8.2 for details and for a proof of the unbiasedness of estimating equation (5.15). The corresponding A-IPCW G-estimator moreover has the desirable property of being doubly-robust in the sense that it is consistent and asymptotically normal if either one of the models $\pi_t(\overline{V}_t;\phi)$ or $m_t(\overline{V}_t;\xi)$ is correctly specified at each time t, but not necessarily both; see Appendix 5.8.3 for a proof of this property.

As compared to the IPCW G-estimator, the A-IPCW G-estimator of (5.15) has an augmentation term that also uses the partial information available from those subjects who are non-administratively censored. At end of follow-up time T_m, the $m_t(\overline{V}_t;\xi)$ term can be written as

$$\begin{aligned} & E\{C_{T_m}U(\psi)|\overline{V}_{T_m}, C_{T_m-1}=1\} \\ = \; & E\{C_{T_m}U(\psi)|\overline{V}_{T_m}, C_{T_m}=1\}\pi_{T_m}(\overline{V}_{T_m};\phi) \\ & +E\{C_{T_m}U(\psi)|\overline{V}_{T_m}, C_{T_m}=0\}\{1-\pi_{T_m}(\overline{V}_{T_m};\phi)\} \\ = \; & E\{U(\psi)|\overline{V}_{T_m}, C_{T_m}=1\}\pi_{T_m}(\overline{V}_{T_m};\phi) \\ = \; & E\{\pi_{T_m}(\overline{V}_{T_m};\phi)U(\psi)|\overline{V}_{T_m}, C_{T_m}=1\} \end{aligned} \tag{5.17}$$

which can be estimated under a model for $\pi_{T_m}(\overline{V}_{T_m};\phi)U(\psi)$ based on subjects remaining uncensored at T_m, and subsequently used to make predictions for subjects with $C_{T_m}=0$ at time point T_m under ICA. This assumption is key to the demonstration of doubly-robustness: $\pi_{T_m}(\overline{V}_{T_m};\phi)$ absorbs the inverse probability weight at time T_m within the summation of $U(\psi)$ in (5.9), thereby reconstructing the full-data estimating function $U_{T_m}(\psi)$ which is independent of C_{T_m} given the past $(\overline{V}_{T_m}, C_{T_m})$. For ease of notation, let

$$E\{\pi_{T_m}(\overline{V}_{T_m};\phi)U(\psi)|\overline{V}_{T_m}, C_{T_m}=1\} \;\equiv\; U^w_{T_m}(\psi) \tag{5.18}$$

$$E\{\pi_t(\overline{V}_t;\phi)U^w_{t+1}(\psi)|\overline{V}_t, C_t=1\} \equiv U^w_t(\psi) \tag{5.19}$$

with $U^w_{T_m}(\psi)$ and U^w_t being functions of $\overline{V}_{T_m}$ and $\overline{V}_t$ respectively. By using the reasoning behind (5.17) at arbitrary $t = T_m, ..., 1$, we have that the $m_t(\overline{V}_t;\xi)$ term can be written as

$$\begin{aligned} E\{C_{T_m}U(\psi)|\overline{V}_t, C_{t-1}=1\} &= E\left[E\{C_{T_m}U(\psi)|\overline{V}_{t+1}, C_t, C_{t-1}=1\}|\overline{V}_t, C_{t-1}=1\right] \\ &= E\{\pi_t(\overline{V}_t;\phi)U^w_{t+1}(\psi)|\overline{V}_t, C_t=1\} \\ &\equiv U^w_t(\psi) \end{aligned} \tag{5.20}$$

Note that functions $U^w_{it}(\psi), t = 1, ..., T_m$, and thus the functions $m_t(\overline{V}_t;\xi)$, can be calculated recursively using the conditional distribution of $\overline{V}_{t+1}$, given $(\overline{V}_t, C_{t-1} = 1)$. Just as with the construction of $U^w_{T_m}(\psi)$, at each t, the augmentation term in (5.15) has the effect that all available information $\overline{V}_t$ of subjects under follow-up at that time ($C_t = 1$) is used, to model either $E(U^w_{t+1}|..)$ if they survived t, or U_{it} if not. The general effect of the term $E\{C_{T_m}U(\psi)|\overline{V}_t, C_{t-1}=1\}$ is therefore that the full data $U_i = \sum_t U_{it}$ estimating equation is reconstructed for subjects with non-administrative drop-out.

5.5 Simulation study

A simulation experiment was conducted to verify the empirical properties of the aforementioned estimators. Samples were created using a previously proposed data generating mechanism for a longitudinal study with dropout (Young et al., 2009). For each subject, we generated $T_0 = -\ln(1-U)/\lambda$ with $U \sim \mathcal{U}(0,1)$ and $\lambda = \exp(-4)$. For $t = 1, .., 10$, we generated (L_t, A_t, C_t) according to $L_t \sim \mathcal{N}[l_0 + l_1(1-U) + l_2A_{t-1}, \sigma^2_t]$, $E(A_t|\overline{A}_{t-1}, \overline{L}_t) = \text{expit}(a_0 + a_1t + a_2L_t)$ and $E(C_t|\overline{C}_{t-1}, \overline{A}_t, \overline{L}_t) = \text{expit}(c_0 + c_1t + c_2L_t + c_3A_t)$, with $(l_0, l_1, l_2, \sigma_t) = (0, 95, 5, 10)$, $(a_0, a_1, a_2) = (-6, 0, .05)$, $(c_0, c_1, c_2) = (-1.5, 0, -.01, -.5)$. The observed survival time T is next created by SNFTM (5.2) and the following algorithm at each t: (1) if $T_0 > \int_0^t \exp(\psi_0 A_t)\text{dt}$ then $Y_t = 0$, (2) else if $T_0 \leq \int_0^t \exp(\psi A_t)\text{dt}$ then $Y_t = 1$, (3) if $Y_t = 0$, then create a new subject-time and repeat above procedure; if $Y_t = 1$

then $T = t + \{T_0 - \int_0^t \exp(\psi A_s \mathrm{ds}\} \exp(-\psi A_t)$, with $\psi = (0, -.25, .25)$. A typical scenario with null exposure effect will yield a sample with 65% of survival times being unobserved due to non-administrative censoring, 65% of survival times of complete cases being unobserved due to administrative censoring, and 44% and 20% cumulative exposure rate in the complete cases and the total group respectively.

Simulated data are analysed under a SNFTM and using the IPCW, A-IPCW, EXPDR-IPCW and EXPDR-A-IPCW G-estimators. Parameters of working models were estimated using discrete-time pooled Logistic regression (D'Agostino et al., 1990) for the models for exposure (5.3) and censoring (5.12), using Cox proportional hazards regression for counterfactual hazard model (5.14), and using linear regression for full data model (5.16). The model for exposure was correctly specified and used all subjects. The model for censoring was either correctly specified following the aforementioned simulation scenario, or misspecified by only including L_t. The model for the counterfactual hazard only included L_t, and only used subjects with observed or administratively censored survival time, with each subject day IPC weighted according to the weights as in (5.11). Full data model (5.16) was fitted on each t and included $\overline{A}_t$ and $\overline{L}_t$ and their interactions as main effects. 95% confidence bounds for $\hat{\psi}$ are obtained via inversion of the score statistic, or the values ψ around $\hat{\psi}$ that give $S(\psi) = \chi^2_{0.95}(p)$, the Chi-square statistic corresponding with cumulative probability of 0.95 and p degrees of freedom. We accounted for estimation of nuisance parameters of working models (if used) (5.3), (5.12) and (5.14) but not of augmentation model (5.16). This was done by calculating $[\Sigma\{U_i(\psi)\}]^{-1}$ in the Score statistic based on estimating function (5.5) in which $g_t\{T_0(\psi)\}$ is replaced by a column vector of all scores of aforementioned models as well as $g_t\{T_0(\psi)\}$, and then by calculating the score statistic for those columns of (5.5) that correspond with parameter η in model (5.4), see Robins (1992) for details. For A-IPCW G-estimators, this will give a conservative confidence interval under a correctly specified model for censoring and a misspecified full data model (Tsiatis, 2006). Each simulation experiment involves 500 repetitions having 5000 subjects each. Estimation algorithms were implemented in STATA and MATA, details of which are given in Appendix 5.8.4.

Table 5.1 summarises the results. All estimators with correctly specified working

models (first four lines of the table) yield median bias well within acceptable range of empirical standard deviation. The IPCW estimator has a higher empirical standard deviation than the A-IPCW estimator, with a reduction of up to 40% when applying augmented estimation. Interestingly, augmented estimation leads to a reduction in empirical variance for the IPCW estimator, but not so much for the EXPDR estimator. As seen in lines 5 and 6 of the table's results, the A-IPCW estimator based on a misspecified working model for censoring yields empirical effect sizes that remain unbiased, unlike the IPCW estimator. This demonstrates the augmented estimator's doubly-robustness property. Such misspecification did not lead to an inflation of variance, with the empirical standard deviation remaining largely unchanged as compared to the augmented estimator with correct IPC weights.

In the last 4 lines of the table, results are shown from scenarios where IPC weights are set to 1, thereby using the augmented estimators' property of being robust against misspecification of these weights. Under this scenario, unbiasedness of augmented estimators was only achieved under very specific forms of the regression model for the full data, see Appendix 5.8.7 for details including diagnostics that we used to evaluate model fit. Interestingly, the A-IPCW estimator with weights set to 1 further improves in terms of empirical variance as compared to the estimator with correctly specified weights. Also, the non-augmented EXPDR estimator already partly adjusts for the bias due to setting censoring weights to 1.

Estimated confidence intervals of estimators with correctly specified working models for censoring roughly achieve nominal coverage. Under IPC weights set to 1, the A-IPCW estimator's variance is estimated conservatively, this is due to not taking into account estimation of full data model parameters for estimation of the asymptotic variance. The EXPDR-A-IPCW estimator under IPC weights set to 1 gives optimistically estimated variance, this is due to either aforementioned reason or its small empirical bias.

	$\psi = 0$			$\psi = -.25$			$\psi = .25$		
Estimator	bias md	MC cov	MC sd	bias md	MC cov	MC sd	bias md	MC cov	MC sd
IPCW	-.004	93	.183	-.011	93	.201	0	95	.161
EXPDR-IPCW	.006	94	.084	-.006	93	.090	.001	95	.078
AIPCW	-.005	96	.101	-.004	96	.117	-.005	95	.100
EXPDR-AIPCW	.006	94	.084	-.006	93	.089	-.001	95	.078
IPCW-MS	-.06	64	.115	-.06	51	.129	-.072	89	.110
AIPCW-MS	-.012	97	.104	-.006	95	.119	-.014	94	.104
IPCW-MS1	-1.24	0	.098	-1.03	0	.024	-1.27	0	.186
AIPCW-MS1	.01	99	.083	.01	95	.095	0	98	.086
EXPDR-IPCW-MS1	-.073	84	.081	-.095	79	.085	-.071	79	.073
EXPDR-AIPCw-MS1	-.016	89	.085	-.034	88	.09	-.025	89	.077

Table 5.1: Performance of Inverse probability of censoring weighted G-estimators for the parameters of a Structural nested failure time model; ψ=true exposure effect; bias md=median bias; MC sd=Simulation standard deviation; MC cov=Simulation 95% CI coverage rate; IPCW=Complete-case inverse probability of censoring weighted; EXPDR=Exposure model doubly-robust; AIPCW=Augmented IPCW; MS(1)=misspecified model for censoring (weights set to 1).

5.6 Application

Proposed estimators are used in the analysis of the attributable effect on mortality of Healthcare-associated infection (HAI) (see Appendix 5.8.5 for background). We use data from the Belgian National surveillance of infections acquired in intensive care units (NSIH-ICU), a study that started in 1997 and is still ongoing. For this article, data collected during period 2007-2012 is analysed, consisting of observations on 14 898 patients admitted to Intensive care unit (ICU). Using a maximum follow-up time in ICU of $T_m = 30$ days, the data contains 107 570 person-days, and is arranged so that there is one observation per person per day that he or she remained in ICU. Keeping with the notation of this article, t will denote the day since admission within ICU, A_t is exposure to Ventilator-associated pneumonia (VAP) at or before day t, L_t is a rich set of variables collected at ICU admission and at each t (listed in Appendix 5.8.5), C_t will denote "remaining in the ICU through day t", and T indicates the survival time.

Working models for exposure, censoring and counterfactual hazard of outcome were fitted as explained in the previous section. We only carried out a model building procedure (using a stepwise selection algorithm) for the models for exposure and censoring, based on available prognostic variables for mortality and HAI. The baseline daily probability function in these models was approximated using a 2nd order polynomial. Full data model (5.16) at each t included as main effects aggregated components of V_t, details of which are given in Appendix 5.8.7. For each estimator, two parametrisations of SNFTM (5.2) for the effect of VAP on mortality are constructed: $\gamma(\overline{A}_t, \overline{L}_t; \psi) = \psi A_t$ where exposure is strictly monotonous and one parameter for the overall effect at all times is estimated, and $\gamma(\overline{A}_t, \overline{L}_t; \psi) = \psi^a I\{\text{cum}(\overline{A}_t) > d\} + \psi^b I\{\text{cum}(\overline{A}_t) \leq d\}$, (with $\text{cum}(\overline{A}_t) = \sum_{s=1}^{t} A_s$) which encodes a separate exposure effect for the 1st $d = 4$ infection days (parameter ψ^b) versus later on (parameter ψ^a). With a two-dimensional causal parameter, $g_t(x)$ in estimating equation (5.5) becomes a two-dimensional vector function, which we chose to be $g_t(x) = (x, x^2)$. Calculation of the counter-

factual administrative censoring time $T_m(\psi)$ following (5.6) then goes as follows:

$$\begin{aligned} T_{m(t,0)}(\psi) &= t-1+(T_m-t+1)\exp\{\psi^a I(\psi^a<0)\}I\{\text{cum}(\overline{A}_t)>d\} \\ &\quad +(T_m-t+1)\exp\{\psi^b I(\psi^b<0)\}I\{\text{cum}(\overline{A}_t)\leq d\} \end{aligned} \tag{5.21}$$

Of 605 (4.1%) patients with one or more episodes of VAP, 151 (25%) died, compared to 1 273 deaths (8.9%) that occurred in 14 293 (95.9%) VAP-free patients. The group of complete cases, meaning those patients with either observed death up to day 30 in the ICU or still alive and remaining in the ICU at that time, contained 1 844 patients (12.4% of all patients) and corresponding 27 319 patient days within the ICU. For these patients, 1 424 deaths and 306 episodes of VAP were observed. Estimated daily conditional probabilities of remaining under follow-up had a range of $[0.22, 0.99]$ across all time points. Once stabilised by probabilities $\pi_t(A_0, L_0; \phi^*)$, this range became $[0.27, 1.7]$. The cumulative stabilised conditional censoring probabilities up to day 30 as defined by the inverse of (5.12) still suffered from a minority of patient days with extremely low cumulative probabilities, having a total min-max range of $[1.41 \times 10^{-6}, 1786]$. Due to this, we were not able to reach converging optimisations for any of the studied estimators, and were forced towards a sensitivity analysis in which IPC weights were truncated to either $[0.2-5]$, $[0.1-10]$ and $[1p-99p]$ ranges (with the latter the 1 to 99 percentile range of weights, corresponding to value range $[0.047-21.4]$), as well as a scenario with weights set to 1. IPC weight truncation followed the procedure described in Appendix 5.8.6.

Results are summarised in Table 5.2, see also Appendix 5.8.8 for preliminary gridsearches of one- and two-parameter G-estimators. Estimators with weights not set to 1 and/or augmented estimators yield lightly protective or neutral one-parameter estimates, for example the EXPDRA-IPCW estimator with weights set to 1 that gives a log survival time ratio (lSR) of VAP-exposed versus -unexposed patient days of -0.14 (95% CI $-0.56, 0.16$). When separated in effects until or after day 4 after onset of infection, most estimators yield effect estimates early after infection that are more protective than those late after onset, for example the aforementioned estimator giving a lSR of -2 (95% CI $-12, -0.15$) early versus

0.11 (95% CI $-0.32, 0.63$) later on. This is except for the A-IPCW estimator with IPC weights set to 1, the results of which show that early infection effects are more harmful than late after infection. However, results for this estimator and weight setting should be taken with caution, because convergence was only obtained by setting a lag effect on the variables encoding exposure in the full data model, with lag size also influencing the one- and two-parameter estimates and their precision (the table gives results using a lag of 4 days). In terms of efficiency, we see that full data augmentation brought by the A-IPCW estimator only improves in the scenario where IPC weights are set to 1. Our results demonstrate this across estimators, for example for the A-IPCW estimator with weights set to 1 having a standard error of 0.08 as compared to the IPCW estimator with a standard error of 0.45, as well as within an estimator across truncation ranges, for example EXPDRA-IPCW estimator with one-parameter standard error 0.1 under IPC weights set to 1 compared to 0.18 under weights truncated towards a [1p-99p] range. Of course, by setting weights to 1, the doubly-robustness property of the augmented estimator will be lost.

5.7 Discussion

The augmented G-estimators for the causal parameters of a SNFTM will be useful when parameter estimates from a standard G-estimator are too variable due to insufficient observations with complete survival time (for example due to censoring of the survival time). Furthermore, because standard G-estimators only use data from subjects with observed survival time or that survived long enough to be administratively censored, it can yield biased results in data with high rates of non-administrative censoring. In such circumstances, the robustness against misspecification of the model for IPC weights is certainly useful, and can provide estimates different from those of the standard G-estimator. Added advantage is that the doubly-robustness offers protection for a 'deliberate' misspecification of the model for censoring weights such as truncation or setting these to 1.

Causal models such as the SNFTM have the property of enabling valid adjust-

Model	Effect	log $\hat{SR}$ (95% CI) (se)			
		1	.2-5	.1-10	1-99p
IPCW	overall	-1.4 (-2.6,-.79)(.45)	-.4 (-.97,.19)(.3)	-.09 (-.89,.71)(.41)	.39 (-.18,1.4)(.39)
	d1-4	-.5 (n/c,-.89)	-.81 (n/c,.72)	-.91 (n/c,1.2)	-.19 (n/c,1.2)
	$>$ d4	-.79 (-1.3,-.29)(.26)	-.17 (-.8,.55)(.35)	.29 (-.83,1.1)(.49)	.75 (.04,1.4)(.33)
EXPDR-IPCW	overall	-.45 (-.66,-.22)(.11)	-.45 (-.74,-.13)(.16)	-.38 (-.78,.07)(.22)	-.15 (-.56,.23)(.2)
	d1-4	.24 (-.1,.51)(.15)	-.94 (n/c,-.11)	-1.6 (n/c,.06)	-3.4 (-11,-.3)(2.8)
	$>$ d4	-.97 (-1.6,-.46)(.29)	-.31 (-.79,.17)(.24)	-.06 (-.68,5)(.3)	.19 (-.31,.68)(.25)
AIPCW	overall	-.12 (-.28,.04)(.08)	-.07 (-.77,.85)(.41)	-.08 (-.95,1.1)(.53)	.13 (-.55,1.1)(.43)
	d1-4	.07 (-.06,.15)(.05)	-.03 (-1.9,.87)(.71)	-.04 (-2.4,1.0)(.87)	-.12 (n/c,1.1)
	$>$d4	-.34 (-.42,-.26)(.04)	-.24 (-1.2,.65)(.46)	-.22 (-1.5,.9)(.61)	.3 (-.58,.98)(.4)
EXPDR-AIPCW	overall	-.28 (-.47,-.09)(.1)	-.42 (-.73,-.07)(.17)	-.35 (-.79,.05)(.21)	-.14 (-.56,.16)(.18)
	d1-4	-.35 (-1.4,.11)(.11)	-1.2 (n/c,-.18)	-1 (n/c,.08)	-2 (-12,-.15)(3)
	$>$d4	-.28 (-.58,.03)(.15)	-.2 (-.68,.21)(.22)	-.14 (-.79,.38)(.3)	.11 (-.32,.63)(.24)

Table 5.2: Effect of Ventilator-associated pneumonia on mortality using Inverse probability of censoring weighted (IPCW) G-estimation under Structural nested accelerated failure time models; $\hat{SR}$=Estimated survival time ratio (exposed versus unexposed); CI=Confidence interval; se=Score standard error; (1,.2-5,.1-10,p99)=Truncation ranges of IPC-weights according to specified minimum-maximum range; IPCW=Complete-case inverse probability of censoring weighted; AIPCW=Augmented IPCW, EXPDR=Exposure model doubly-robust, n/c=not converged.

ment for time-dependent confounding in contrast to stratification-based methods such as Logistic or Cox proportional hazards regression. Under the usual assumptions, both SNFTMs (used here) and Marginal structural proportional hazards models (MSPHMs) (Robins, 2000; Hernàn et al., 2001) yield relative risk estimates with causal interpretation. MSPHMs, while also applying IPC weighted estimation to correct for dependent censoring, adjust for (time dependent) confounding of the exposure-outcome association by separately calculated Inverse probability of exposure (IPE) weights. The use of the SNFTM has the following advantages over the MSPHM: (1) The MSPHM infers on exposure histories such as "contrary to what is observed, assign exposure regime $\overline{a}$ to all subjects" which may be unrealistic when studying an exposure such as HAI. In contrast, the SNFTM restricts attention to the subgroup of exposed subjects to calculate the exposure-free survival time. By doing so, the SNFTM's findings translate directly in an easy to use message such as "by preventing a patient from getting infected, his or her survival time will be increased or reduced by a factor X". (2) By directly exploiting SRA in the G-estimation procedure, the SNFTM avoids the need for IPE weights. These can introduce bias in the MSPHM's results when the models for exposure are wrongly specified or when the fitted models yield extreme weights for particular subjects. In spite of this, a disadvantage of SNFTMs relative to MSPHMs is that no standard software exists for routine use of the G-estimation procedure. When survival times are subject to administrative censoring, back-calculation of counterfactuals in the presence of re-censoring can also lead to non-smooth estimating functions (Joffe et al., 2012; Vock et al., 2013). On top of this, implementation of the augmentation term calls for the use of an estimating equation approach and corresponding optimisation routines, which might be even more tedious to implement.

The protective to neutral relative risks that we found for the effect of infection on mortality are unexpected from a clinical point of view. This can be explained by insufficient adjustment for prognostic factors of the mortality-censoring relation: assuming that exposure is protective for censoring and harmful for mortality, and assuming an unmeasured common prognostic factor U that affects censoring and outcome in the same way as exposure (thereby violating ICA), then restricting the analysis to subjects under follow-up will create a negative non-causal association

between C and Y, and as a consequence a protective non-causal effect of A on Y. Therefore, collecting extra prognostic factors for the mortality-censoring relationship might be a valid future strategy. An alternative is to try to avoid IPC weighting, and choose a competing risk approach, for example as done by Bekaert et al. (2009) in a similar setting as this study but working under a MSPHM.

5.8 Appendix

5.8.1 Unbiasedness of the Complete-case IPCW estimator

We first demonstrate unbiasedness of (5.9) when using unstabilised weights, defined as:

$$W_{it}^{\text{unstab}} = \prod_{s=t}^{X_i} \pi_s(\overline{V}_{is};\phi) \tag{5.22}$$

by which we have:

$$\begin{aligned}
& E\left\{ \frac{C_{iT}}{\prod_{s=t}^{X_i} \pi_s(\overline{V}_{is};\phi)} U_{it}(\psi) \right\} \\
= \;& E\left\{ \prod_{s=t}^{X_i} \frac{I(C_{is}=1)}{\pi_s(\overline{V}_{is};\phi)} U_{it}(\psi) \right\} \\
= \;& E\left[E\left\{ \prod_{s=t}^{X_i} \frac{I(C_{is}=1)}{\pi_s(\overline{V}_{is};\phi)} U_{it}(\psi) \middle| \overline{V}_{iX_i}, \overline{C}_{iX-1}=1 \right\} \right] \\
= \;& E\left[\frac{E(C_{iX}=1|\overline{V}_{iX_i}, \overline{C}_{iX-1}=1)}{\pi_{X_i}(\overline{V}_{is};\phi)} E\left(\frac{\prod_{s=t}^{X_i-1} I(C_{is}=1)}{\prod_{s=t}^{X_i-1} \pi_s(\overline{V}_{is};\phi)} U_{it}(\psi) \middle| \overline{V}_{iX_i}, \overline{C}_{iX-1}=1 \right) \right] \\
= \;& E\left\{ \prod_{s=t}^{X_i-1} \frac{I(C_{is}=1)}{\pi_s(\overline{V}_{is};\phi)} U_{it}(\psi) \right\} \\
= \;& .. \\
= \;& E\left\{ I(C_{it-1}=1) U_{it}(\psi) \right\} \\
= \;& 0
\end{aligned} \tag{5.23}$$

with ICA being used in the third equality, and the last equality due to $U_{it}(\psi)$ defined in (5.10) having mean zero given $(\overline{V}_t, C_{t-1} = 1)$, and showing unbiasedness of this estimating function when applying unstabilised weights W_{it}^{unstab}.

When using stabilised weights W_{it}^{stab} instead, the above derivation becomes

$$\begin{aligned} E\left\{ C_{iT_m} \prod_{s=t}^{X_i} \frac{\pi_s(V_{i0})}{\pi_s(\overline{V}_{is})} U_{it}(\psi) \right\} &= E\left\{ I(C_{it-1} = 1) \prod_{s=t}^{X_i} \pi_s(V_{i0}) U_{it}(\psi) \right\} \\ &= 0 \end{aligned} \tag{5.24}$$

again because $U_{it}(\psi)$ has mean zero given $(\overline{V}_t, C_{t-1} = 1)$, of which V_0 is part. Using derivation (5.24), it can be shown that stabilisation probabilities $\pi_s(V_0)$ can be extended to $\pi_t(\overline{V}_t)$, therefore including all available information up to time t. However, such approach might be cumbersome, because it necessitates building of separate models at each time point.

5

5.8.2 Derivation of the AIPCW estimator

We follow Tsiatis (2006) (Section 10.3, Theorem 10.4) for this derivation. A minimal requirement for having an efficient estimator is that (locally, under some model) its influence function is orthogonal to the tangent space for the parameters indexing the censoring model $\pi_t(\overline{V}_t; \phi)$. This tangent space consists of all functions of the form

$$\Lambda_C = \left[\sum_t d_t(\overline{V}_t) \{ C_t - \pi_t(\overline{V}_t; \phi) \} C_{t-1} \right] \tag{5.25}$$

We thus seek to find functions d_{0t} satisfying

$$\begin{aligned} 0 = E\Big(\Big[C_T U(\psi) + \sum_t d_{0t}(\overline{V}_t) \{ C_t - \pi_t(\overline{V}_t; \phi) \} C_{t-1} \Big] \\ \times \sum_t d_t(\overline{V}_t) \{ C_t - \pi_t(\overline{V}_t; \phi) \} C_{t-1} \Big) \text{ for all } d_t \end{aligned} \tag{5.26}$$

the right hand side part of which can be written as

$$E\Big[C_T U(\psi)\sum_t d_t(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}C_{t-1}\Big] \tag{5.27}$$

$$+\quad E\Big[\sum_t d_{0t}(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}C_{t-1}\sum_s d_s(\overline{V}_s)\{C_s-\pi_t(\overline{V}_t;\phi)\}C_{s-1}\Big] \tag{5.28}$$

By looking at arbitrary $d_s(\overline{V}_s)\{C_s-\pi_s(\overline{V}_s;\phi)\}C_{s-1}$ within $\sum_t d_t(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}C_{t-1}$ and conditioning on $(\overline{V}_s, C_{s-1})$, (5.28) gives:

$$E\Big(C_{s-1}E\big[\sum_t d_{0t}(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}C_{t-1}d_s(\overline{V}_s)(C_s-\pi_s(\overline{V}_s;\phi))\big|\overline{V}_s,C_{s-1}\big]\Big) \tag{5.29}$$

First, note that

$$\begin{aligned} & E\left(C_{s-1}E\Big[\sum_{t=1}^{s-1} d_{0t}(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}C_{t-1}d_s(\overline{V}_s)\{C_s-\pi_s(\overline{V}_s;\phi)\}\Big|\overline{V}_s,C_{s-1}\Big]\right) \\ = \quad & E\Big(C_{s-1}\sum_{t=1}^{s-1} d_{0t}(\overline{V}_t)\{1-\pi_t(\overline{V}_t;\phi)\}C_{t-1}d_s(\overline{V}_s)E\big[\{C_s-\pi_s(\overline{V}_s;\phi)\}\big|\overline{V}_s,C_{s-1}\big]\Big) \end{aligned} \tag{5.30}$$

which equals 0, due to $E[\{C_s-\pi_s(\overline{V}_s;\phi)\}|\overline{V}_s, C_{s-1}=1]=0$.

Further,

$$\begin{aligned} & E\left(C_{t-1}E\Big[\sum_{t=s+1}^{T} d_{0t}(\overline{V}_t)\{C_t-\pi_t(\overline{V}_t;\phi)\}d_s(\overline{V}_s)\{C_s-\pi_s(\overline{V}_s;\phi)\}C_{s-1}\Big|\overline{V}_t,C_{t-1}\Big]\right) \\ = \quad & E\Big(C_{t-1}\sum_{t=s+1}^{T} d_s(\overline{V}_s)\{1-\pi_s(\overline{V}_s;\phi)\}C_{s-1}d_{0t}(\overline{V}_t)E\big[\{C_t-\pi_t(\overline{V}_t;\phi)\}\big|\overline{V}_t,C_{t-1}\big]\Big) \end{aligned} \tag{5.31}$$

which equals 0, due to $E[\{C_t-\pi_t(\overline{V}_t;\phi)\}|\overline{V}_t, C_{t-1}=1]=0$.

Finally, the term in (5.29) corresponding to $t = s$ is

$$\begin{aligned} & E\Big(C_{s-1}E\big[d_{0s}(\overline{V}_s)d_s(\overline{V}_s)\{C_s - \pi_s(\overline{V}_s;\phi)\}^2\big|\overline{V}_s, C_{s-1}\big]\Big) \\ = \; & E\Big(C_{s-1}d_{0s}(\overline{V}_s)d_s(\overline{V}_s)E[\{C_s - \pi_s(\overline{V}_s;\phi)\}^2|\overline{V}_s, C_{s-1}]\Big) \\ = \; & E\Big[d_{0s}(\overline{V}_s)d_s(\overline{V}_s)C_{s-1}\text{var}\{C_s|\overline{V}_s, C_{s-1}\}\Big] \\ = \; & E\Big[d_{0s}(\overline{V}_s)d_s(\overline{V}_s)C_{s-1}\pi_s(\overline{V}_s;\phi)\{1 - \pi_s(\overline{V}_s;\phi)\}\Big] \end{aligned} \tag{5.32}$$

Similarly, (5.27) gives

$$\begin{aligned} & E\Big(C_{t-1}E\big[C_T U(\psi)\sum_t d_t(\overline{V}_t)\{C_t - \pi_t(\overline{V}_t;\phi)\}\big|\overline{V}_t, C_{t-1}\big]\Big) \\ = \; & E\big[C_{t-1}\sum_t d_t(\overline{V}_t)\{1 - \pi_t(\overline{V}_t;\phi)\}E\{C_T U(\psi)|\overline{V}_t, C_{t-1}\}\big] \end{aligned} \tag{5.33}$$

Combined, we obtain that (5.26) equals

$$\begin{aligned} & E\big[\sum_t d_t(\overline{V}_t)\{1 - \pi_t(\overline{V}_t;\phi)\}C_{t-1}E\{C_T U(\psi)|\overline{V}_t, C_{t-1} = 1\} \\ & + \sum_t d_{0t}(\overline{V}_t)d_t(\overline{V}_t)C_{t-1}\pi_t(\overline{V}_t;\phi)\{1 - \pi_t(\overline{V}_t;\phi)\}\big] \\ = \; & E\big(\sum_t d_t(\overline{V}_t)\{1 - \pi_t(\overline{V}_t;\phi)\}C_{t-1} \\ & \times\big[E\{C_T U(\psi)|\overline{V}_t, C_{t-1} = 1\} + d_{0t}(\overline{V}_t)\pi_t(\overline{V}_t;\phi)\big]\big) \end{aligned} \tag{5.34}$$

This equals 0 whenever

$$E\{C_T U(\psi)|\overline{V}_t, C_{t-1} = 1\} = -d_{0t}(\overline{V}_t)\pi_t(\overline{V}_t;\phi) \tag{5.35}$$

or when

$$d_{0t}(\overline{V}_t) = -\frac{E\{C_T U(\psi)|\overline{V}_t, C_{t-1} = 1\}}{\pi_t(\overline{V}_t;\phi)} \tag{5.36}$$

yielding estimating function:

$$C_T U(\psi) + \sum_t \frac{E\{C_T U(\psi)|\overline{V}_t, C_{t-1}=1\}}{\pi_t(\overline{V}_t;\phi)}\{\pi_t(\overline{V}_t;\phi) - C_t\}C_{t-1} \tag{5.37}$$

5.8.3 Proof of doubly-robustness of the AIPCW estimator

Under the true censoring model $\pi_t(\overline{V}_t;\phi)$, the estimating function for ψ is unbiased due to $E\{C_T U(\psi)\} = 0$ (see Appendix 5.8.1) and

$$E\big\{\pi_t(\overline{V}_t;\phi) - C_t\big|\overline{V}_t, C_{t-1}=1\big\} \;=\; 0, \tag{5.38}$$

which also holds when $\pi_t(\overline{V}_t;\phi)$ is stabilised by $\pi_t(\overline{V}_0)$ as in (5.11). We now show that they are also unbiased if the censoring model is misspecified, provided that the model for the conditional distribution of V_{t+1} given $(\overline{V}_t, C_{t-1}=1)$ holds at each time t. First, using

$$U^{w*}_{iT_m}(\psi) \;=\; E\big\{\pi^*_{T_m}(\overline{V}_{iT_m};\phi^*)U_i(\psi)\big|\overline{V}_{iT_m}, C_{iT_m}=1\big\} \tag{5.39}$$

$$U^{w*}_{it}(\psi) \;=\; E\big\{\pi^*_t(\overline{V}_{it};\phi^*)U^{w*}_{i,t+1}(\psi)\big|\overline{V}_{it}, C_{it}=1\big\} \tag{5.40}$$

with $\pi^*_t(\overline{V}_{it};\phi^*)$ the misspecified censoring probabilities, and $U^{w*}_{i,T_m}(\psi)$ and $U^{w*}_{i,t}(\psi)$ the models using both the misspecified probabilities as well as the estimating function $U(\psi)$ that is weighted for the misspecified $\pi^*_t(\overline{V}_{it};\phi^*)$.

The A-IPCW estimating function can be rewritten as

$$\begin{aligned} & E\Bigg[C_{T_m}U(\psi) + \sum_{t=1}^{T_m-1} U^{w*}_t(\psi)C_{t-1}\Big\{1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)}\Big\} \\ & + C_{T_m-1}U^{w*}_{T_m}(\psi) - C_{T_m-1}C_{T_m}\frac{U^{w*}_{T_m}(\psi)}{\pi^*_{T_m}(\overline{V}_{T_m};\phi^*)}\Bigg] \end{aligned} \tag{5.41}$$

$$\begin{aligned} = \; & E\Bigg(E\Bigg[C_{T_m}U(\psi) + C_{T_m-1}U^{w*}_{T_m}(\psi) - C_{T_m-1}C_{T_m}\frac{U^{w*}_{T_m}(\psi)}{\pi^*_{T_m}(\overline{V}_{T_m};\phi^*)} \\ & + \sum_{t=1}^{T_m-1} U^{w*}_t(\psi)C_{t-1}\Big\{1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)}\Big\}\Bigg|\overline{V}_{T_m}, C_{T_m-1}\Bigg]\Bigg) \end{aligned} \tag{5.42}$$

$$
\begin{aligned}
&= E\Bigg(E\Bigg[C_{T_m} U(\psi) - C_{T_m} \frac{E\{\pi^*_{T_m}(\overline{V}_{T_m};\phi^*) U(\psi) | \overline{V}_{T_m}, C_{T_m}=1\}}{\pi^*_{T_m}(\overline{V}_{T_m};\phi^*)} \Bigg| \overline{V}_{T_m}, C_{T_m-1} \Bigg] \\
&\quad + C_{T_m-1} U^{w*}_{T_m}(\psi) + \sum_{t=1}^{T_m-1} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg) \qquad (5.43) \\
&= E\Bigg(E\Bigg[C_{T_m} U(\psi) - E\{C_{T_m} U(\psi) | \overline{V}_{T_m}, C_{T_m}=1\} \Bigg| \overline{V}_{T_m}, C_{T_m-1} \Bigg] \\
&\quad + C_{T_m-1} U^{w*}_{T_m}(\psi) + \sum_{t=1}^{T_m-1} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg) \qquad (5.44) \\
&= E\Bigg[C_{T_m-1} U^{w*}_{T_m}(\psi) + \sum_{t=1}^{T_m-1} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg] \qquad (5.45) \\
&= E\Bigg[C_{T_m-1} U^{w*}_{T_m}(\psi) + C_{T_m-2} U^{w*}_{T_m-1}(\psi) - C_{T_m-2} C_{T_m-1} \frac{U^{w*}_{T_m-1}(\psi)}{\pi^*_{T_m-1}(\overline{V}_{T_m-1};\phi^*)} \\
&\quad + \sum_{t=1}^{T_m-2} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg] \qquad (5.46) \\
&= E\Bigg[E\Bigg\{ C_{T_m-1} U^{w*}_{T_m}(\psi) - C_{T_m-1} \frac{U^{w*}_{T_m-1}(\psi)}{\pi^*_{T_m-1}(\overline{V}_{T_m-1};\phi^*)} \Bigg| \overline{V}_{T_m-1}, C_{T_m-2} \Bigg\} \\
&\quad + C_{T_m-2} U^{w*}_{T_m-1}(\psi) + \sum_{t=1}^{T_m-2} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg] \qquad (5.47) \\
&= E\Bigg(E\Bigg[C_{T_m-1} U^{w*}_{T_m}(\psi) - E\{C_{T_m-1} U^{w*}_{T_m}(\psi) | \overline{V}_{T_m-1}, C_{T_m-1}\} \Bigg| \overline{V}_{T_m-1}, C_{T_m-2} \Bigg] \\
&\quad + C_{T_m-2} U^{w*}_{T_m-1}(\psi) + \sum_{t=1}^{T_m-2} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg) \qquad (5.48) \\
&= E\Bigg[C_{T_m-2} U^{w*}_{T_m-1}(\psi) + \sum_{t=1}^{T_m-2} U^{w*}_t(\psi) C_{t-1} \Big\{ 1 - \frac{C_t}{\pi^*_t(\overline{V}_t;\phi^*)} \Big\} \Bigg] \qquad (5.49) \\
&= .. \\
&= E\Big\{ C_0 U^{w*}_1(\psi) \Big\} \qquad (5.50)
\end{aligned}
$$

At time T_m, we use the fact that, under a correct model for the conditional distribution of $V_{[T_m+1]}$ given $(\overline{V}_{T_m}, C_{T_m-1}=1)$, the terms $C_{T_m}U(\psi)$ and $C_{T_m}U^{w*}_T(\psi)/\pi^*_{T_m}(\overline{V}_{T_m};\phi^*)$ are equal and can be dropped (see line 5.45). At times $t=0,...,T_m-1$, under a

correct model for the conditional distribution of $V_{[t+1]}$ given $(\overline{V}_t, C_{t-1} = 1)$, the terms $C_t U_{t+1}^{w*}(\psi)$ and $C_t U_t^{w*}(\psi)/\pi_t^*(\overline{V}_t; \phi^*)$ are equal and can be dropped (see line 5.49 for $t = T_m - 1$). From times $t = T_m - 1$ until 1, we use ICA by letting $U_{t+1}^{w*}(\psi)$ within $C_t U_{t+1}^{w*}(\psi)$ be extrapolated to all contributions with $C_t = 1$, as in the first line of (5.48) for $t = T_m - 1$. The remaining term $E\{C_0 U_1^{w*}(\psi)\}$ in (5.50) is the average complete-case estimating function $U_i(\psi)$ for which the misspecified censoring weights are absorbed recursively at each t through multiplication with $\pi_t^*(\overline{V}_t; \phi^*)$. This estimating equation uses all subjects (due to $C_0 = 1$), which makes it formally a full data estimating function that has mean zero.

5.8.4 Algorithm to construct the AIPCW estimator and implementation of estimators in STATA/MATA

In practice, the augmented term of the estimator that solves (5.15) will be constructed as follows.

1. Fit model (5.12) for the censoring mechanism and calculate the censoring probabilities $\pi_t(\overline{V}_t; \phi)$. Note that these are also calculated to determine the cumulative probabilities of remaining uncensored in the IPCW G-estimator that solves (5.9).

2. Fit models for U_t^w defined by (5.18) and (5.19), recursively for times $t = T_m, .., 1$, and starting with the $U(\psi)$ contributions derived for survival times $T \geq T_m$. This can be done by linear regression models as shown in the main paper. Under ICA at each time t, for both subgroups $(C_t = 1, C_{t-1} = 1)$ and $(C_t = 0, C_{t-1} = 1)$, this model is then used to calculate predicted values of $U_t^w(\psi)$, which are subsequently used in a model for the prediction of $U_{t-1}^w(\psi)$.

3. Finally, solve the A-IPCW estimator for ψ using estimating equation (5.15).

To allow automatic and direct optimisation (as opposed to a manual and iterative grid-search) of the G-estimate for ψ, we implemented above steps (2) and (3) into STATA version 10's matrix programming language MATA (StataCorp LP, College

Station, TX, USA), resulting in the algorithm given below. Using known censoring weights π_t and exposure residuals $A - P(A_t = 1|\overline{A}_{t-1}, .)$ (estimated using regular STATA), the algorithm is called upon in MATA for:

1. Construction of re-censored counterfactual survival times $X_{t,0}(\psi)$ and survival indicator $\delta_0(\psi)$ [using function `gestXdtgp()`],
2. Construction of IPCW (5.9), EXPDR-IPCW (with $g_t\{X_{t,0}(\psi)\}$ based on 5.13), A-IPCW and EXPDR-A-IPCW (5.15) estimating equations (using functions `gestUtgp1()`, `gestXtgpccdr1()`, `gestdda12d()` and `gestdda12-ccdr1()` respectively),
3. Nelder-Mead optimisation of the Score test statistic (see main paper section 5.3.2) towards a minimum, and
4. Estimation of 95% confidence limits and standard errors by gridsearch of Score test statistic.

For EXPDR estimators, hazard functions are estimated by going back to STATA within the MATA algorithm setting a particular ψ.

MATA functions rely on the following matrices (with n the number of subjects, N the number of subjectdays): Y ($n \times T_m$, outcome Y), A ($n \times T_m$, exposure A), R [$n \times T_m$, exposure residual from estimating equation (5.5)], CCUM [$n \times T_m$, IPC weights (5.11)], I ($n \times 1$, complete-case indicator C_{T_m}), CT ($n \times T_m$, $C_{T_m}C_t$), `Xcensp` ($N \times 1$, scores for estimating the parameters of the censoring model), `Xexpp` ($N \times 1$, scores for estimating the parameters of the exposure model), CP ($n \times T_m$, $1 - C_t$ with $C_t = 1$ recoded to missing, for use by augmentation model), CPP ($n \times T_m$, $1 - C_t$), L ($nT_m \times q_l$, time-dependent confounders), L0 ($nT_m \times q_{l_0}$, time-independent confounders), C ($n \times T_m$, stabilised probability of remaining under follow-up at day t).

```
*IPCW Estimating Equation and Score Statistic
capture mata:mata drop gest_Xdtgp()
mata
real matrix gest_Xdtgp(real scalar q)
```

```
{

  if (q<-13.3) q=-13.3

  q11=q

  external Y, A, CT

  r=.0001
  col=cols(Y)
  row=rows(Y)

  m=J(col,col,1)
  for(i=1; i<=col; i++) {
    for(j=1; j<=col; j++) {
      if (i>j) m[i,j]=0
    }
  }

  n=J(col,col,1)
  for(i=1; i<=col; i++) {
    for(j=1; j<=col; j++) {
      if (i>=j) n[i,j]=0
    }
  }

  Aq=q11*A
  Ap=exp(Aq)

  At=Ap

  Yp = Y:*At
  Ytgp = round(editvalue(Yp,.,0)*m',r)

  q31=q11
  if (q31>=0) q31=0
  Ctgp=J(1,col,0)
  for(j=1; j<=col; j++) {

    Ctgpsi1=(col-j+1)*exp(q31)
    if (Ctgpsi1>=col-j+1) Ctgpsi1=col-j+1

    Ctgp[.,j]=round(Ctgpsi1,r)

  }

  P = Ytgp:<Ctgp
  P0 = 1:-P
  Xtgp = P0:*Ctgp + P:*Ytgp

  dtgp = P:*CT

  return(Xtgp,dtgp)

}

end

capture mata:mata drop gest_Utgp1a()

mata
```

```
real matrix gest_Utgp1a(real scalar q)
{

  external R

  D = 1
  X = gest_Xdtgp(q)[,(1::30)]
  U = D:*X

  Uts = U:*R

  return(Uts)

}

end

capture mata:mata drop gest_Utgp1()

mata

real matrix gest_Utgp1(real scalar q)
{

  external CCUM

  D = 1
  Xa = gest_Utgp1a(q)
  U = D:*Xa

  Uts = CCUM:*U

  return(Uts)

}

end

capture mata:mata drop gestssp()

mata

real matrix gestssp(real scalar q)
{
  external I

  Uts1=gest_Utgp1(q)
  Uts1=editvalue(Uts1,.,0)
  Uts1=rowsum(Uts1)
  Uts1=editvalue(I:*Uts1,.,0)

  return(Uts1)

}

end

capture mata:mata drop gestsp5()

mata
```

```
real scalar gestsp5(real scalar q)
{

  external Xcensp, Xexpp, Cx

  if (Cx==1) Up=Xcensp, Xexpp, gestssp(q)
  if (Cx==0) Up=Xexpp, gestssp(q)
  Xcols=cols(Up)

  n=rows(Up)

  Ups=colsum(Up[,Xcols])

  sigma=n*variance(Up)
  isigma=invsym(sigma)

  t=Ups*isigma[Xcols,Xcols]*Ups'

  return(t)

}

end

*EXPDR–IPCW Estimating Equation and Score Statistic

capture mata:mata drop gest_Xtgp_ccdr1()

mata

real matrix gest_Xtgp_ccdr1(real scalar q)
{

  external Y

  stata("qui:cap drop Xt")
  stata("qui:cap drop dt")

  Xdt=gest_Xdtgp(q)
  nvs=vec(Xdt[,(1::30)]'),vec(Xdt[,(31::60)]')
  Ytt=vec(Y')
  nvss=select(nvs,Ytt[,1]:~=0)

  idx = st_addvar(("double","int"),("Xt","dt"))
  st_store(.,idx,nvss)

  stata("qui:cap drop phcb")
  stata("qui:cap drop pxb")
  stata("qui:cap drop phc")
  stata("qui:cap drop cres*")
  stata("qui:cap drop Uti")
  stata("qui:compress")
  stata("qui:stset Xt if cT==1&am==0 [pw=cw0cumit2], failure(dt==1)")
  stata("qui:stcox l_1* l0*, basechazard(phcb) esr(cres*) nohr")
  stata("qui:predict pxb , xb")
  stata("qui:gen phc=phcb*exp(pxb)")
  stata("qui:gen Uti=(dt-phc)*cw0cumit2*res_e*cT*(1-am)")

  stata("preserve")
  stata("sort case day")
```

```
  stata("keep case Uti cres*")
  stata("collapse (sum) Uti cres*, by(case)")
  stata("drop case")
  stata("order cres* Uti")
  stata("mata:Xcox=st_data(.,.)")
  stata("restore")

  st_dropvar(("Xt","dt","phcb","pxb","phc"))

  external Xcox

  return(Xcox)

}

end

capture mata:mata drop gestsp5_ccdr1()

mata

real scalar gestsp5_ccdr1(real scalar q)
{

  external Xcensp, Xexpp

  Up=Xcensp, Xexpp, gest_Xtgp_ccdr1(q)
  Xcol=cols(Up)

  n=rows(Up)
  Ups=colsum(Up)

  sigma=n*variance(Up)
  isigma=invsym(sigma)

  t=Ups[,Xcol]*isigma[Xcol,Xcol]*Ups[,Xcol]'

  return(t)

}

end

*AIPCW Estimating Equation and Score Statistic

mata:l=4

capture mata:mata drop gestdda12d()

mata

real matrix gestdda12d(real rowvector q)
{

  external CPP, CP, L, L0, X, C, Y, Y2, A, I, l

  Lf=L

  col=cols(Y)
  row=rows(Y)
```

```
Cdr=CPP:/C
Cdr=1:-Cdr

R1=CPP:~=.
R1=editvalue(R1,0,.)

R2=CP
R2=editvalue(R2,0,.)

Uts=editvalue(gest_Utgp1(q),.,0)
Utsr=Uts
for(i=1; i<=col; i=i+1) {
  Utsr[.,i]=rowsum(Uts[.,(1::i)])
}

Ars=A
for(i=1; i<=col; i=i+1) {
  Ars[.,i]=rowsum(A[.,(1::i)])
}

EUt=J(row,col,.)
EUt[.,col]=Utsr[.,col]

for(i=col;i>=3;i=i-1) {

  Uti=EUt[.,i]:*R2[.,i]:*C[.,i]
  Utii=select(Uti,Uti[,1]:~=.)

  At=A[.,i]
  Arst=Ars[.,i]
  L0i=select(L0[,(1::2)],X[.,2]:==i)
  AL0i=At:*L0i
  Lfi=select(Lf,X[.,2]:==i)
  Yt=Y2[.,i]
  if (i>l) {
    Alt=A[.,i-l]
    Arslt=Ars[.,i-l]
  }

  L0ia=L0i:*R2[.,i]
  Yi=Yt:*R2[.,i]
  Ali=Alt:*R2[.,i]
  Arsli=Arslt:*R2[.,i]
  Lfia=Lfi:*R2[.,i]

  L0ii=select(L0ia,L0ia[,1]:~=.)
  Yii=select(Yi,Yi[,1]:~=.)
  Lfii=select(Lfia,Lfia[,1]:~=.)
  Alii=select(Ali,Ali[,1]:~=.)
  Arslii=select(Arsli,Arsli[,1]:~=.)

  if (i>l) {
    Xii=Alii,Arslii,L0ii,Lfii,J(rows(Utii),1,1)
    Xi=(Alt,Arslt,L0i,Lfi):*R1[.,i],J(rows(Uti),1,1)
  }
  else {
    Xii=L0ii,Lfii,J(rows(Utii),1,1)
    Xi=(L0i,Lfi):*R1[.,i],J(rows(Uti),1,1)
  }

  b=invsym(Xii'*Xii)*Xii'*Utii
```

```
    EUt[.,i]=Xi*b

    if (i>3) {
      EUtim=Y2[,i-1]:*editvalue(Utsr[,i-1],.,0) + (1:-Y2[,i-1]):*editvalue(EUt[,i
          ],.,0)
      EUt[,i-1]=EUtim
    }

  }

  Utdr=editvalue(EUt:*Cdr,.,0)

  Uts=I:*Uts
  Uts=editvalue(Uts,.,0)

  U=Uts:+Utdr
  Up=rowsum(U)

  return(Up)

}

end

capture mata:mata drop gestdp5()

mata

real scalar gestdp5(real scalar q)
{

  external R, Xcensp, Xexpp, Cx

  if (Cx==1)  Ud_p=Xcensp, Xexpp, gestdda12d(q)
  if (Cx==0)  Ud_p=Xexpp, gestdda12d(q)

  Xcols=cols(Ud_p)

  n1=rows(Ud_p)

  U=colsum(Ud_p)

  sigma=n1*variance(Ud_p)
  isigma=invsym(sigma)

  t=U[,Xcols]*isigma[Xcols,Xcols]*U[,Xcols]'

  return(t)

}

end

*EXPDR–AIPCw Estimating Equation and Score Statistic

capture mata:mata drop gestdda12_ccdr1()

mata

real matrix gestdda12_ccdr1(real rowvector q)
```

```
{
  external CPP, CP, L, L0, X, C, Y, Y2, A, I

  Lf=sqrt(L)

  col=cols(Y)
  row=rows(Y)

  Cdr=CPP:/C
  Cdr=1:-Cdr

  R1=CPP:~=.
  R1=editvalue(R1,0,.)

  R2=CP
  R2=editvalue(R2,0,.)

  Uts0=gest_Xtgp_ccdr1(q)
  Uts0c=cols(Uts0)

  Uts=editvalue(Uts0[,Uts0c],.,0)
  Utsr=Uts

  Ars=A
  for(i=1; i<=col; i=i+1) {
    Ars[.,i]=rowsum(A[.,(1::i)])
  }

  EUt=J(row,col,.)
  EUtR=EUt
  EUt[.,col]=Utsr

  for(i=col;i>=3;i=i-1) {

    Uti=EUt[.,i]:*R2[.,i]:*C[.,i]
    Utii=select(Uti,Uti[,1]:~=.)

    At=A[.,i]
    Li=select(L,X[.,2]:==i)
    Lfi=select(Lf,X[.,2]:==i)
    ALfi=At:*Lfi
    ALLfi=At:*Lfi:*Lfi
    ALLLfi=At:*Lfi:*Lfi:*Lfi
    L0i=select(L0,X[.,2]:==i)
    AL0i=At:*L0i

    Ai=At:*R2[.,i]
    L0ia=L0i:*R2[.,i]
    AL0ia=AL0i:*R2[.,i]
    ALfia=ALfi:*R2[.,i]
    ALLfia=ALLfi:*R2[.,i]
    ALLLfia=ALLLfi:*R2[.,i]

    Aii=select(Ai,Ai[,1]:~=.)
    L0ii=select(L0ia,L0ia[,1]:~=.)
    AL0ii=select(AL0ia,AL0ia[,1]:~=.)
    ALfii=select(ALfia,ALfia[,1]:~=.)
    ALLfii=select(ALLfia,ALLfia[,1]:~=.)
    ALLLfii=select(ALLLfia,ALLLfia[,1]:~=.)
```

```
      Xii=Aii, ALfii, ALLfii, AL0ii, J(rows(Aii),1,1)
      Xi=(At, ALfi, ALLfi, AL0i):*R1[.,i]
      Xi=Xi, J(rows(Uti),1,1)

      b=invsym(Xii'*Xii)*Xii'*Utii

      EUt[.,i]=Xi*b

      if (i>3) {
        EUtim=Y2[,i-1]:*Utsr + (1:-Y2[,i-1]):*editvalue(EUt[,i],.,0)
        EUt[,i-1]=EUtim
      }

    }

    Utdr=editvalue(EUt:*Cdr,.,0)

    Uts=I:*Uts
    Uts=editvalue(Uts,.,0)

    U=Uts:+Utdr
    Up=rowsum(U)

    return(Uts0[,(1::Uts0c-1)],Up)

}

end

capture mata:mata drop gestdp5_ccdr1()

mata

real scalar gestdp5_ccdr1(real scalar q)
{

    external Xcensp, Xexpp, Cx

    if (Cx==1)  Ud_p=Xcensp, Xexpp, gestdda12_ccdr1(q)
    if (Cx==0)  Ud_p=Xexpp, gestdda12_ccdr1(q)

    Xcols=cols(Ud_p)
    Ud_p=Ud_p[,Xcols]
    Xcols=cols(Ud_p)

    n1=rows(Ud_p)

    U=colsum(Ud_p)

    sigma=n1*variance(Ud_p)
    isigma=invsym(sigma)

    t=U[,Xcols]*isigma[Xcols,Xcols]*U[,Xcols]'

    return(t)

}

end

*optimisation of score statistic
```

```
*- score statistic function gests_est()
*- Nelder Mead starting value rs1_s and stepsize rs1_d

cap mata:mata drop si()

mata

  void si(todo,x,y,g,H)
  {
    y=gests_est(x)
  }

end

capture mata:mata drop opt_nm()

mata

real matrix opt_nm(real rowvector q)
{

  S=optimize_init()
  optimize_init_which(S, "min")
  optimize_init_evaluator(S, &si())
  optimize_init_evaluatortype(S, "d0")
  optimize_init_technique(S, "nm" )

  optimize_init_params(S, q[1])
  optimize_init_nmsimplexdeltas(S, q[2])

  optimize_init_tracelevel(S, "tolerance")

  optimize_init_conv_ptol(S, .0001)

  optimize_init_conv_maxiter(S, 50)

  rs=optimize(S)

  return(rs)

}

end

noi:mata

  rs=rs1_s
  rd=rs1_d
  rsd=rs1_s+rs1_d

  f0=gests_est(rs)
  f0m=gests_est(rsd)

  if (f0<100) {

  while (mreldif(f0m,f0)>.001) {

rs,f0,f0m,mreldif(f0m,f0),rd

    f0m=f0
    rsm=rs
```

```
    rs=round(opt_nm((rs,rd)),.001)
    f0=gests_est(rs)

    rd=round(abs((rsm:-rs)/2),.001)

    if (rd<.002) rd=0.002
    if (rd>rs1_d) rd=rs1_d

    // if (f0<1) nm_d=(.5,.01)

  }
rs,f0

  }
  else {

    rs=.

  }

end

*variance calculation
*- generic score statistic function gests_est()

mata

  rs1_5=.
  rs1_95=.
  rs1_e=.

  rs2_5=-1
  rs2_95=-1
  rs2_e=-1

  s=.00001

  if (rs1~=.) {

  f0=round(gests_est(rs1),s)
  f01=round(gests_est(rs1+0.5),s)
  incb=round((f01-f0)/.5,s)
incb

  }

  ptol=10e-4
  p=1
  chisq=round(invchi2(p,.95),.01)
chisq

  if (f0<=chisq) {

        cirows=800
        incb=round(((chisq-f0)/incb)/4,s)
incb

        mu=J(cirows,5,.)
        su=round(rs1,s)
        f=f0
        nc=0
```

```
        inc=incb
        if (abs(su)<=inc) inc=1.1*abs(su)
        j=1
        mu[j,1]=round(su,s)
        mu[j,2]=round(f,s)
        mu[j,3]=mreldif(f,chisq)
        mu[j,5]=round(inc,s)
        mu[j,4]=round(inc*mreldif(f,chisq),s)
        while (mu[j,2]<=chisq & mu[j,3]>ptol & j<cirows & nc==0) {

          j=j+1

          mu[j,1]=round(mu[j-1,1]+mu[j-1,4],s)
          mu[j,2]=round(gests_est(mu[j,1]),s)
          mu[j,3]=mreldif(mu[j,2],chisq)
          if (j>=5) {
            if (mu[j,3]/mu[j-4,3]>=.9) inc=1.1*inc
            if (mu[j,3]/mu[j-4,3]<=.1) inc=.9*inc
          }
          mu[j,5]=round(inc,s)
          mu[j,4]=round(inc*mu[j,3],s)
          ru=mu[j,1]

          if (j>=50) {
            if (mu[j,2]==mu[j-49,2]) nc=1
          }
mu[j,]
        }
mu[(1::j),.]
        if (j<cirows&nc==0) rs1_95=ru

        ml=J(cirows,5,.)
        sl=round(rs1,s)
        f=f0
        nc=0

        inc=round(incb,s)
        if (abs(su)<=inc) inc=1.1*abs(su)
        j=1
        ml[j,1]=round(sl,s)
        ml[j,2]=round(f,s)
        ml[j,3]=mreldif(f,chisq)
        ml[j,5]=round(inc,s)
        ml[j,4]=inc*mreldif(f,chisq)
        while (ml[j,2]<=chisq & ml[j,3]>ptol & j<cirows & nc==0) {

          j=j+1

          ml[j,1]=round(ml[j-1,1]-ml[j-1,4],s)
          ml[j,2]=round(gests_est(ml[j,1]),s)
          ml[j,3]=mreldif(ml[j,2],chisq)
          if (j>=5) {
            if (ml[j,3]/ml[j-4,3]>=.9) inc=1.1*inc
            if (ml[j,3]/ml[j-4,3]<=.1) inc=.9*inc
          }
          ml[j,5]=round(inc,s)
          ml[j,4]=round(inc*ml[j,3],s)

          rl=ml[j,1]
```

```
            if (j>=50) {
              if (ml[j,2]==ml[j-49,2]) nc=1
            }
ml[j,]
          }
ml[(1::j),.]
          if (j<cirows&nc==0) rs1_5=rl

          rs1_e = (rs1_95 - rs1_5)/(2*1.96)

  }

end
```

5.8.5 Attributable effect of Healthcare-associated infection on mortality

Although the estimation of this effect has been looked at in many studies and research articles, the results remain controversial with for example relative risk estimates for the mortality effect of pneumonia acquired in the ICU - a common type of HAI - ranging from being harmful to neutral. This has raised the long-standing research question whether patients in the ICU tend to die ”from” or ”with” infection (Carlet, 2001), the former statement implying that infection indeed causally affects survival, the latter that it is merely an effect of other events that eventually lead to death. Research for a precise and well-defined attributable effect of infection on mortality and into a correct method for its estimation is needed because it provides healthcare professionals with the exact information on the costs (both in terms of mortality as morbidity) that arise when a patient acquires a HAI, and because it provides input (in terms of results to be expected) for hospitals wanting to implement infection control strategies for the prevention of HAI (Frank, 2007).

Exposure to infection being non-randomised and time-dependent implies that the analysis for the attributable effect must adjust for time-dependent confounders of the exposure-mortality relationship. This is challenging, both in terms of finding a methodology that gives interpretable effect estimates and in obtaining data containing information to enable sufficient adjustment. As mentioned above, standard stratification-based methods, such as the adjusted Cox proportional

hazards model, are known to give biased effects when these are stratified for time-dependent confounders that act as cause and effect of exposure at different time points. Such models are therefore particularly problematic when aiming to estimate lagged effects of exposure to infection on mortality, such as the effect on mortality at time t of onset of infection up to (at least) d days previously, and this with the aim to get insight in the burden of infection immediately or late after its onset.

In terms of finding valid data to estimate the attributable effect of infection, ongoing interest in the prevention of ICU-acquired infection has lead to many patient-based surveillance studies in which besides baseline information collected at the patient's admission to the ICU also daily information on clinical exposures and outcomes has become available. Because these daily measured variables can be considered as proxy information for the patient's daily changing health status, they are candidates for adjusting the crude effect of infection on mortality. However, when relying on ICU surveillance studies for studying a patient's survival, a further challenge is that only data on a patient's follow-up within the ICU are available. This implies that survival times of patients that recovered and were at some point discharged from the ICU will be unobserved or censored. This type of censoring is typically non-administrative because for each ICU patient it may happen at a different time-point, and dependent on his or her health status at that time-point. The consequence is also that only a minority of patients that died in the ICU will have an actually observed survival time. Typical ICU follow-up data of survival will also include administrative censoring at a time-point T_m, after which the remaining subjects of the original cohort are too low-numbered and specific to justify further follow-up.

The "NSIH-ICU" follows the "Hospitals in Europe link for infection control through surveillance (HELICS)" protocol which is the common standard for European networks wanting to conduct surveillance of ICU-acquired infections (Suetens et al., 2007; Mertens et al., 2013). ICUs participating in national surveillance need to collect data on the occurrence of ICU-acquired infections for all patients admitted to the ICU during 3 consecutive months. Besides this, specific follow-up data on each patient's daily exposure to a set of clinical exposure variables needs to be

Baseline	Daily-varying
gender	mechanical ventilation
multiple trauma	central vascular catheter
acute coronary care	presence of naso or oro-intestinal tube
age	feeding through a naso or oro-intestinal tube
SAPS II score	parenteral feeding
prior surgery	stoma feeding
type of admission	nasal/oral intubation
AB use in 48h before or after admission	tracheotomy intubation

Table 5.3: L_t variables available for adjusting the attributable effect of ICU-acquired infection on mortality; Age categories $< 40, 40-59, 60-69, 70-74, \geq 80$; SAPS=Simplified acute physiology, categories $< 20, 20-39, 40-59, \geq 60$; Type of admission categories Medical/ Scheduled surgery/ Unscheduled surgery; AB use=Antibiotic, categories None/ Prophylactic/ Therapeutic/ Combination; Surgery categories None/ Elective/ Urgent.

collected; see Table 5.3 for a description of all collected variables.

5.8.6 Procedure for weight truncation

To prevent extreme weights, IPC weights were truncated in the following way. Going backwards from the last day to the first, we will truncate these probabilities to fit within the range $[1/w^{\text{trunc}}, w^{\text{trunc}}]$, that is, whenever $\prod_T^t \pi_s(\overline{V}_s)/\pi_s(\overline{V}_0)$ exceeds w^{trunc} or is lower than $1/w^{\text{trunc}}$, we will put $\pi_t(\overline{V}_t) = \pi_t(\overline{V}_0)$ at days $1, .., t$, which will stabilise the calculation of (5.11) at these time points. If necessary, this procedure will truncate for each subject his or her $\pi_t(\overline{V}_t)$ and corresponding $\pi_t(\overline{V}_t) = \pi_t(\overline{V}_0)$ values during the first few days of follow-up. The truncated probabilities will affect the A-IPCW estimator both through IPC weights W_t in the term for complete cases as well as through the censoring probabilities $\pi_t(\overline{V}_t)$ in the augmentation term for all subjects. The set of weight truncation ranges $[1/w^{\text{trunc}}, w^{\text{trunc}}]$. w^{trunc} was chosen to be $(5, 10, 21.4)$, the first two values arbitrarily, while the last value corresponded to a truncation of inverse cumulative stabilised conditional censoring probabilities outside the 99 percentiles range (discussed in main paper).

5.8.7 Full data modelling

To facilitate the full data modelling process of the Simulation study, we constructed residual plots for each of the $T_m = 10$ time-points at which a full data model (5.16) was estimated. Construction of these plots proved to be useful specifically under the simulation scenarios with IPC weights set to 1, with unbiasedness of augmented estimators A-IPCW and EXPDR-A-IPCW thus completely relying on correct specification of the full data model. Plots were constructed for the converging value of ψ, and showed for a particular full data model the residual versus the fitted value. Observations where plotted according to exposure status at t (the time at which the model was constructed) and/or at T (the time of the subject's outcome or administrative censoring). Figures 5.1-5.4 show these plots for A-IPCW and EXPDR-A-IPCW estimators, each figure starting with full data model at $T_m = 10$. For both A-IPCW and EXPDR-A-IPCW estimators under the scenario where IPC weights were set to 1, we compare the residual plots generated under a "general" full data model with main effects (A, L, AL) that yielded an empirically biased estimator with those generated under a "specific" full data model giving unbiased (or least-biased) empirical estimators. Plots are those of the first run of a simulation, with a true exposure effect $\psi_0 = -0.25$.

For both estimators A-IPCW and EXPDR-A-IPCW, the plots were useful in detecting non-linearities in the residuals generated by a "general" full data model at time $t = 10$ with main effects (A, L, AL), see plots at "day 10" of Figures 5.1 and 5.3. This was resolved by constructing a full data model based on polynomial main effects of the confounder L, therefore resulting in main effects (L, LL, LLL, A, LA, LLA) and $(A, LA, LLA, LLLA)$ for A-IPCW and EXPDR-A-IPCW estimators, respectively (see plots at "day 10" of Figures 5.2 and 5.4). Allowing for nonlinearities in the full data model also has the effect of making the range of residuals more compact, as seen when going from a min-max range $[-2.1, 0.7]$ in the first plot of Figure 5.1 to range $[-0.5, 0.2]$ in the first plot of Figure 5.2. Such compacter range of residuals might explain why A-IPCW and EXPDR-A-IPCW estimators under IPC weights set to 1, besides being unbiased, also have lowest empirical variance.

Even under a full data model that gives unbiased empirical results for the estimator, we see regions with outlying observations in the residual plots, indicating that lack of fit of a full data model does not necessarily affect the unbiasedness of an estimator. This can be seen in the plots at day 1 of Figures 5.2 and 5.4, in which we see outlying regions of observations for both $A = 0$ and $A = 1$, with a clearly defined region for observations having $(A_t = 0, A_T = 1)$, marking those observations that are unexposed at t but gaining exposure later on. Using information beyond time t in a full data regression model at time t would violate ICA, the question therefore remains whether it is possible at all to find full data models that can handle such outlying residuals, and if so, how this would affect the estimator's empirical properties (bias as well as variance).

The EXPDR-A-IPCW estimator only gave unbiased results under a full data model with prognostic variable L strictly entering the model through interactions with A. A hypothesis for this is that the EXPDR-A-IPCW estimator is based on functional $g\{T_0(\psi)\}$ that uses a proportional hazards regression model having L as main effect, and therefore can be considered as already partly adjusting for L, but this needs to be investigated.

Figures 5.5 and 5.6 show similar residual plots for full data models used for the Application's A-IPCW and EXPDR-A-IPCW estimators, respectively. Also here, we give results for the full data models constructed when IPC weights were set to 1, and this from day 30 to day 3 (augmentation stops at day 3 because no loss to follow-up occurs during the first 2 days), and using $3-$day intervals. For the A-IPCW estimator, despite absence of nonlinearities in the residual plot at day 30, outlying residuals for observations under exposure are visible at all days until day 6. These are due to the lag-effect (4 days) being set on the variables encoding exposure status in the full data models, and which were omitted from the models for days $6 - 3$. The last residual plot (at day 3) for this estimator shows a small group of observations under absence of exposure where residuals are linearly related to predictions, which indicating lack of fit for these observations. Such problems were not seen for the EXPDR-A-IPCW estimator, despite the difficulty of this estimator's full data model to adequately model observations under absence of exposure.

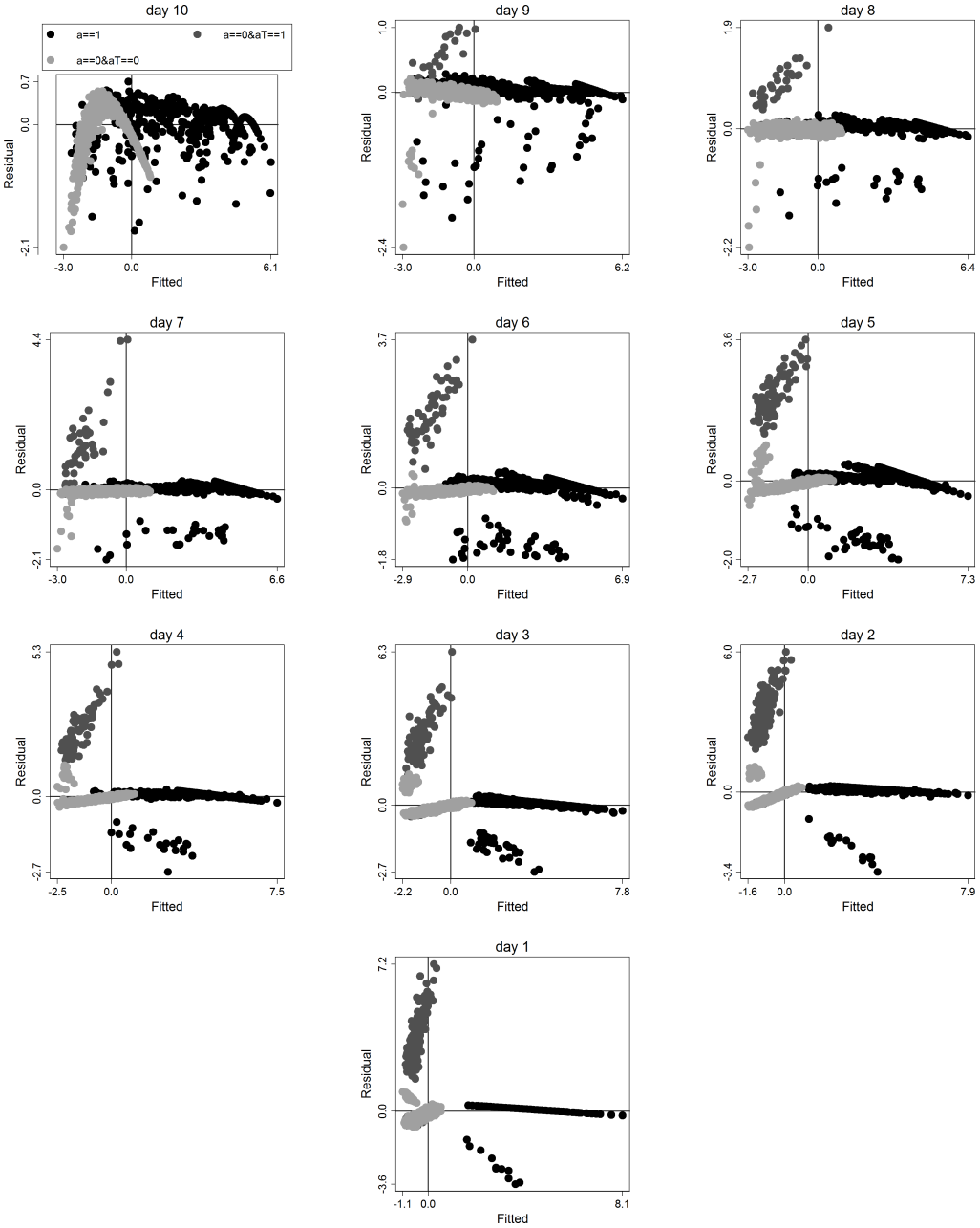


Figure 5.1: Simulation: plot of residual versus predictions for the full data regression model as used by the AIPCW estimator with censoring weights set to 1, example of one simulation repetition, full data model main effects (L, A, LA).

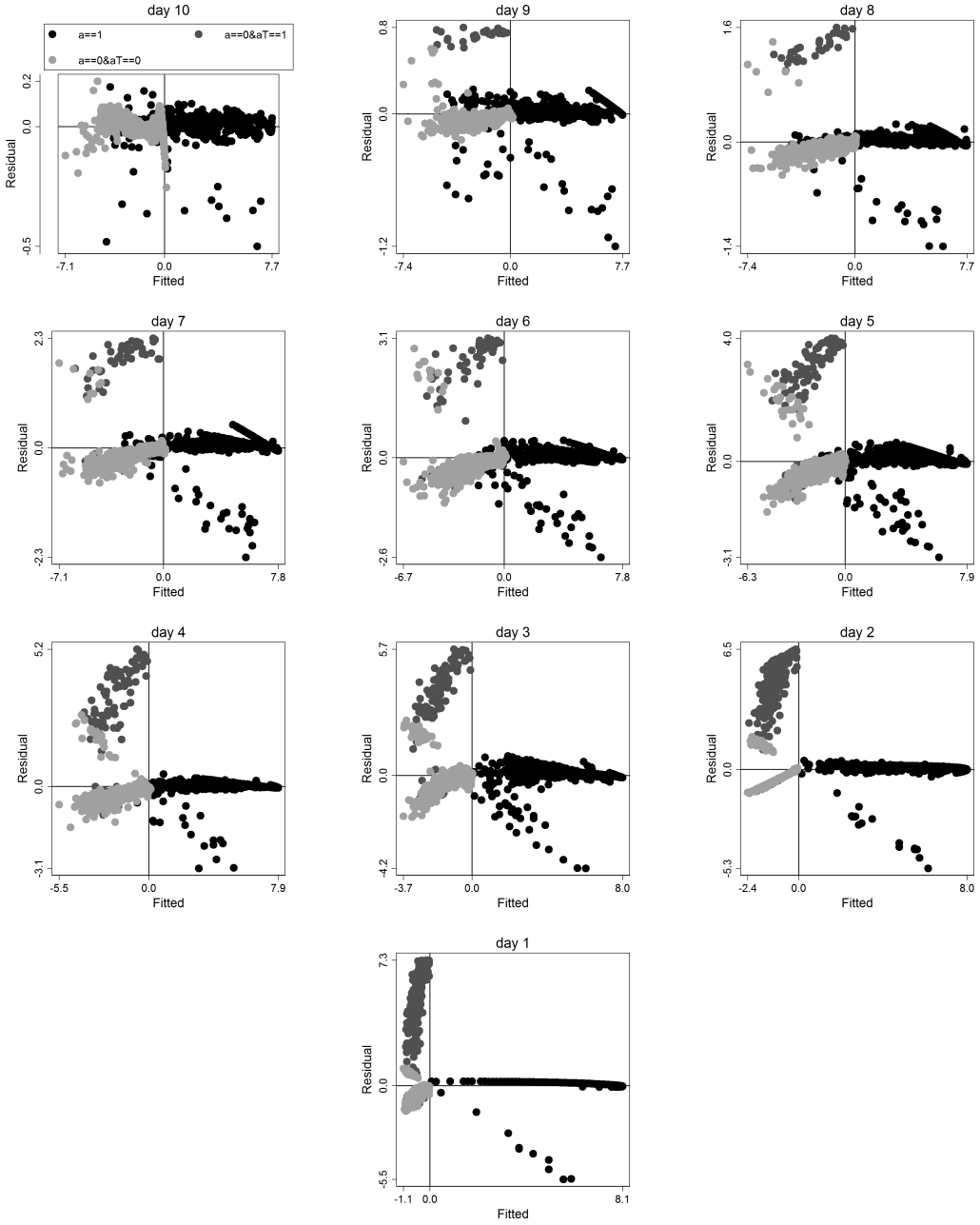


Figure 5.2: Simulation: plot of residual versus predictions for the full data regression model as used by the AIPCW estimator with censoring weights set to 1, example of one simulation repetition, full data model main effects (L, LL, LLL, A, LA, LLA).

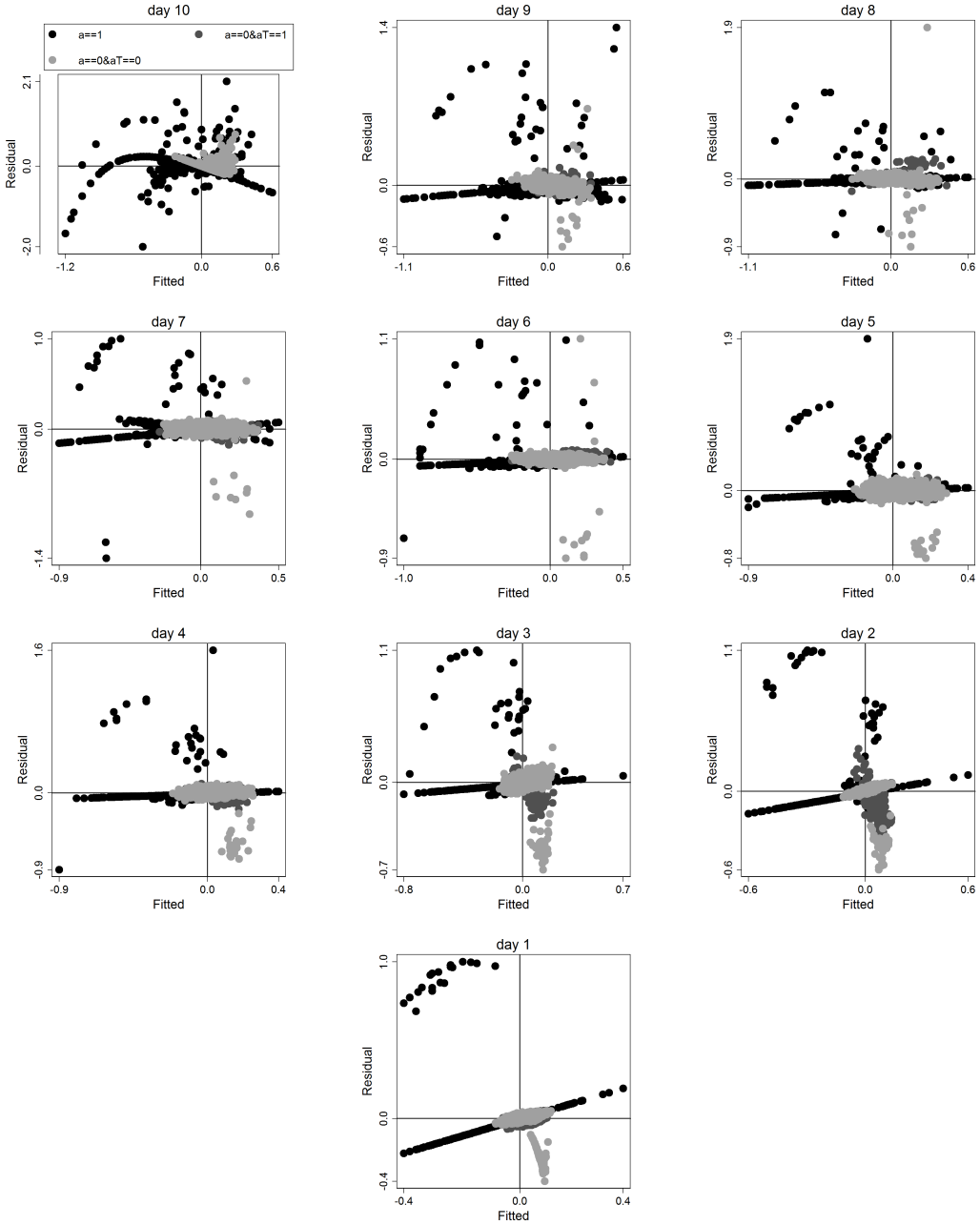


Figure 5.3: Simulation: plot of residual versus predictions for the full data regression model as used by the EXPDR-AIPCW estimator with censoring weights set to 1, example of one simulation repetition, full data model main effects (L, A, LA).

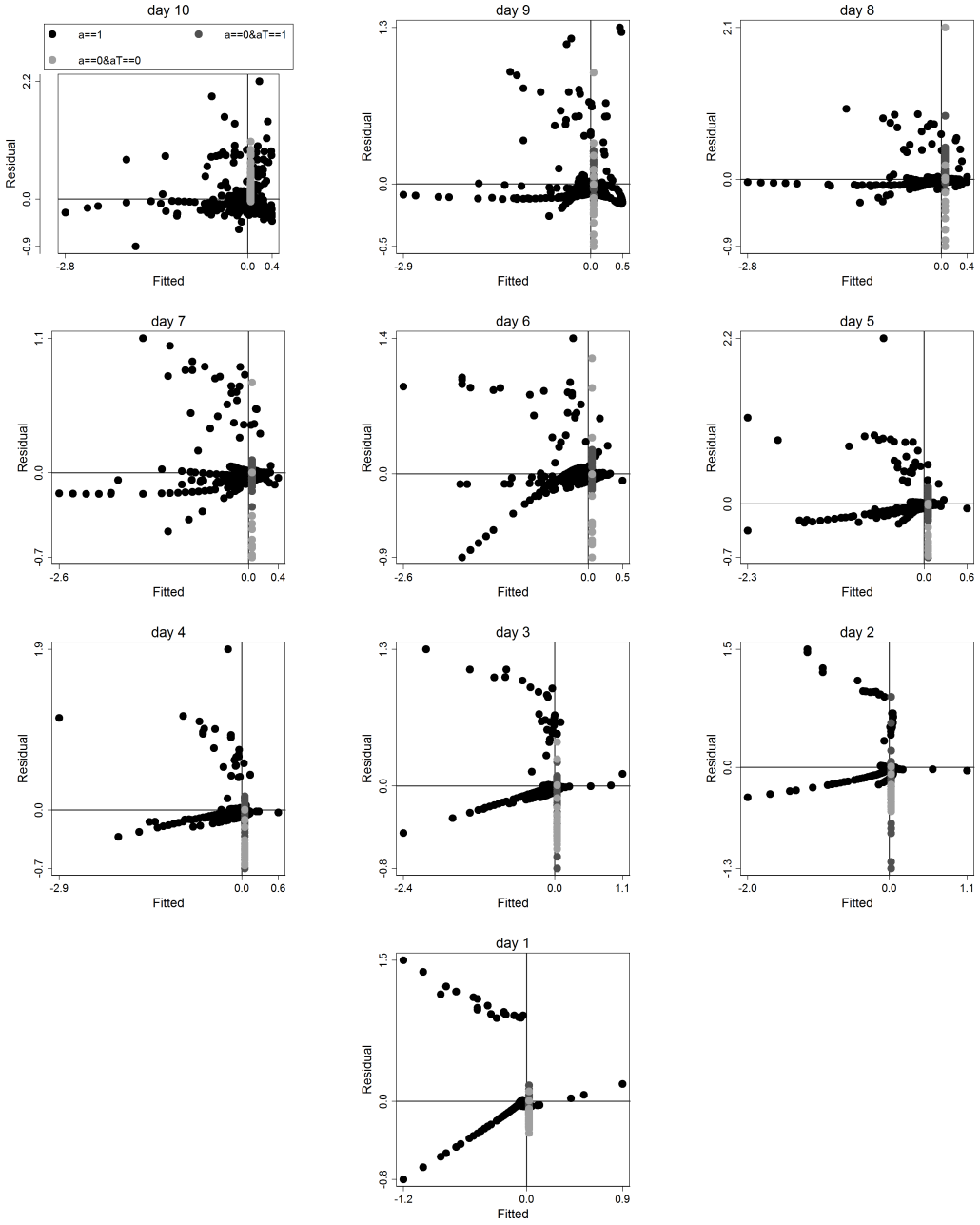


Figure 5.4: Simulation: plot of residual versus predictions for the full data regression model as used by the EXPDR-AIPCW estimator with censoring weights set to 1, example of one simulation repetition, full data model main effects $(A, LA, LLA, LLLA)$.

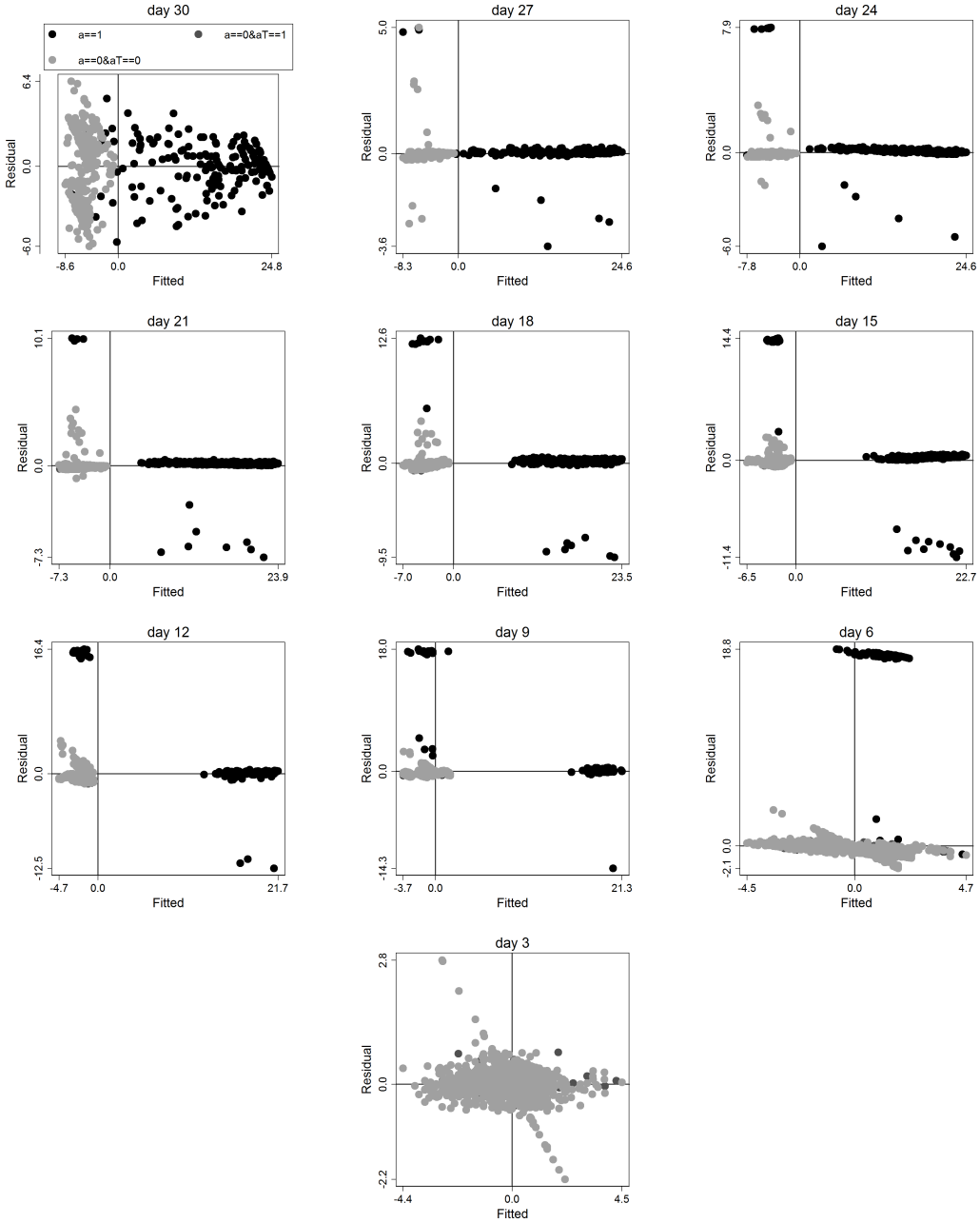


Figure 5.5: Application: plot of residual versus predictions for the full data regression model as used by the AIPCw estimator with censoring weights set to 1 and with full data model main effects $(A, \overline{A}, L, L_0)$.

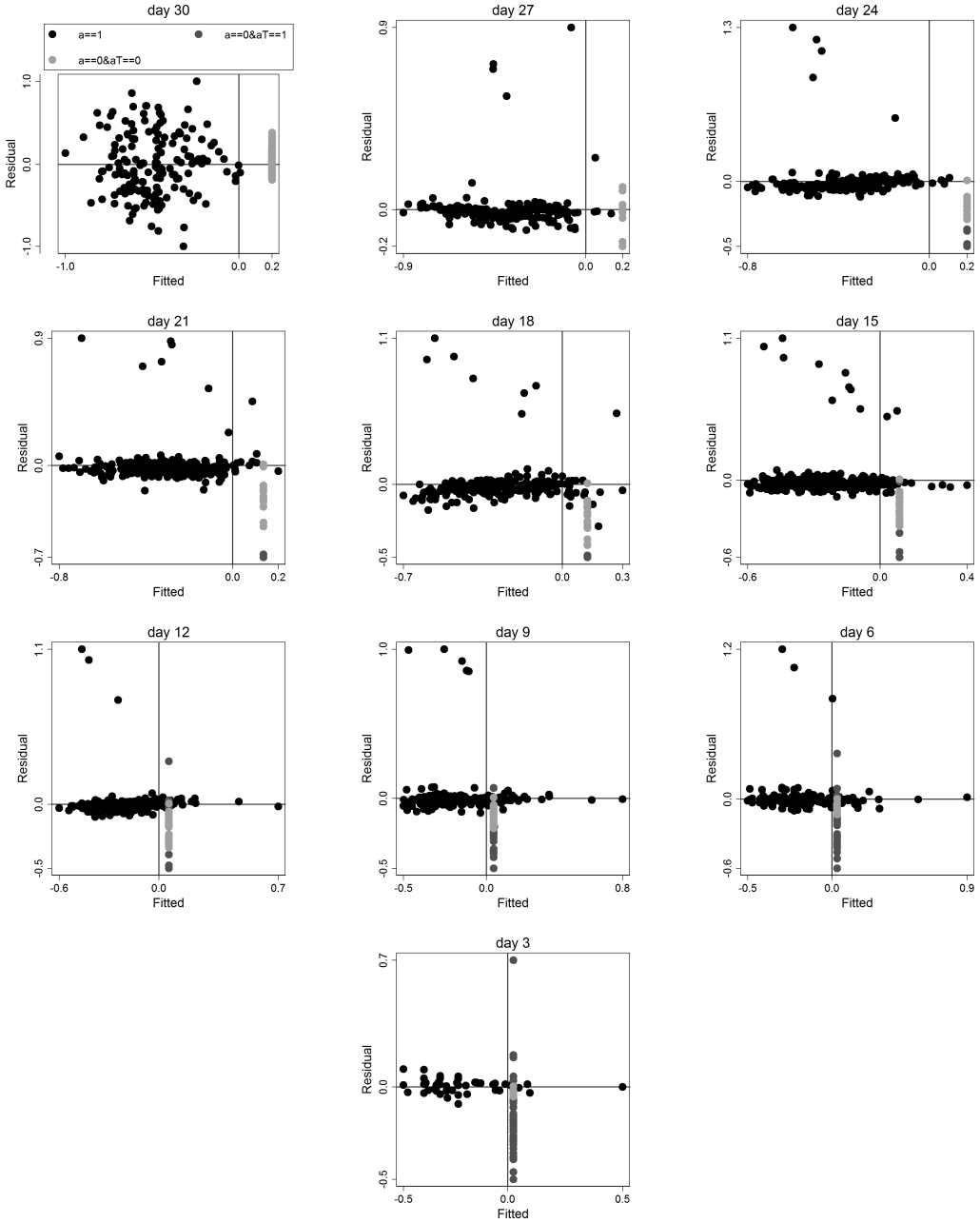


Figure 5.6: Application: plot of residual versus predictions for the full data regression model as used by the EXPDR-AIPCW estimator with censoring weights set to 1 and with full data model main effects (A, LA, LLA, L_0A).

5.8.8 Application: preliminary gridsearches for one- and two-parameter estimators

Figures 5.7-5.14 show results of preliminary gridsearches that were obtained during optimisation of the Application's one- and two-parameter IPCW, EXPDR-IPCW, A-IPCW, and EXPDR-A-IPCW estimators, and this for all studied truncation scenarios. Roots of these gridsearches were subsequently used as starting values in a Nelder-Mead optimisation for each estimator, using half the gridsearch stepsize as optimisation stepsize.

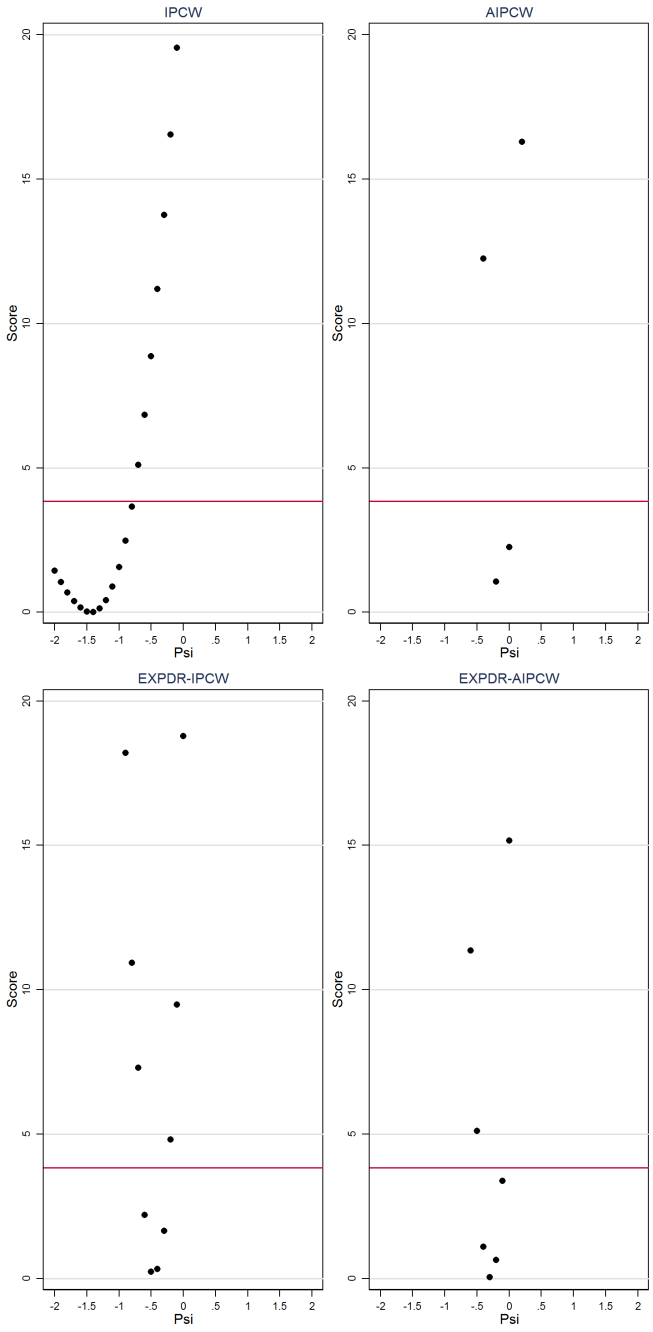


Figure 5.7: plot of Score statistic S versus candidate ψ values for the overall effect of Ventilator-associated pneumonia on mortality, IPC weight truncation [1]; IPC=Inverse probability of censoring.

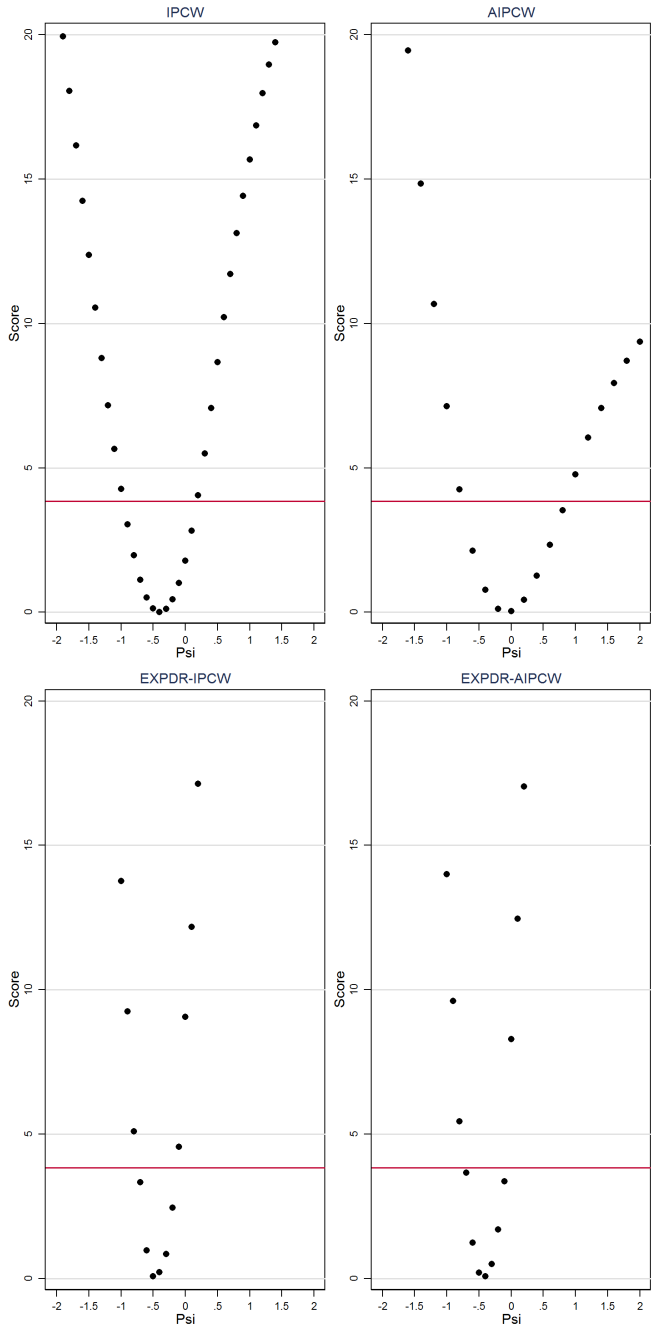


Figure 5.8: plot of Score statistic S versus candidate ψ values for the overall effect of Ventilator-associated pneumonia on mortality, IPC weight truncation [.2-5]; IPC=Inverse probability of censoring.

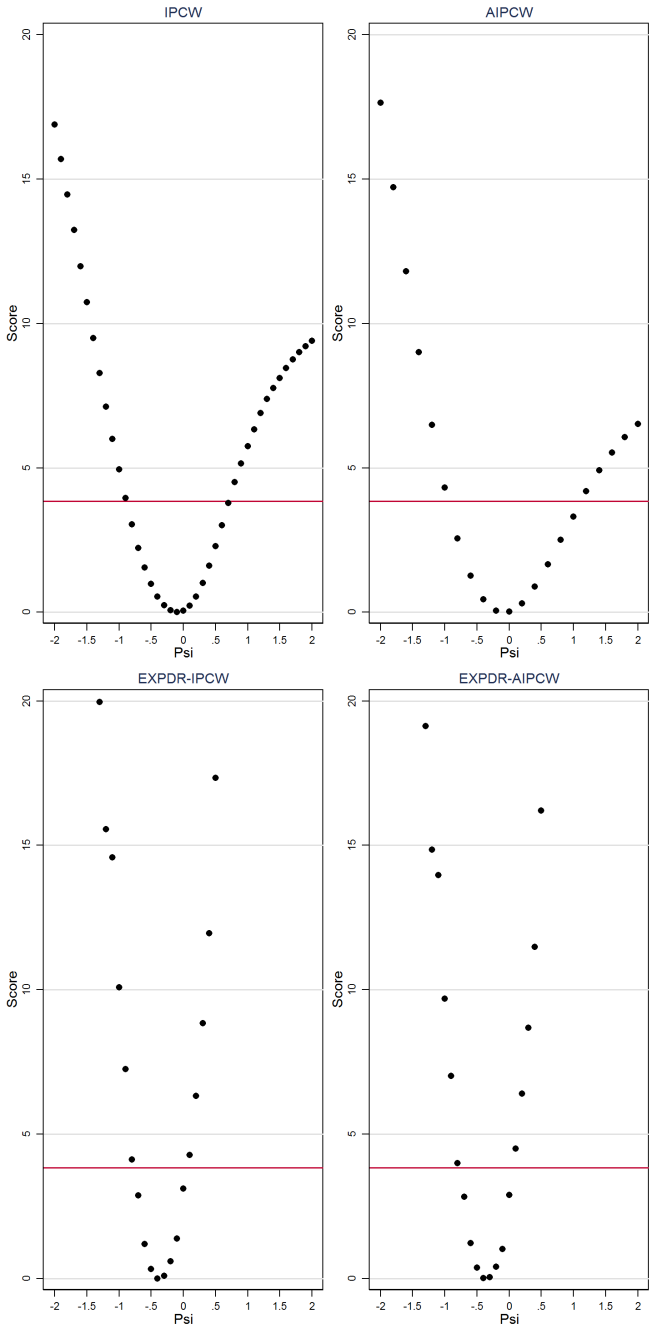


Figure 5.9: plot of Score statistic S versus candidate ψ values for the overall effect of Ventilator-associated pneumonia on mortality, IPC weight truncation [.1-10]; IPC=Inverse probability of censoring.

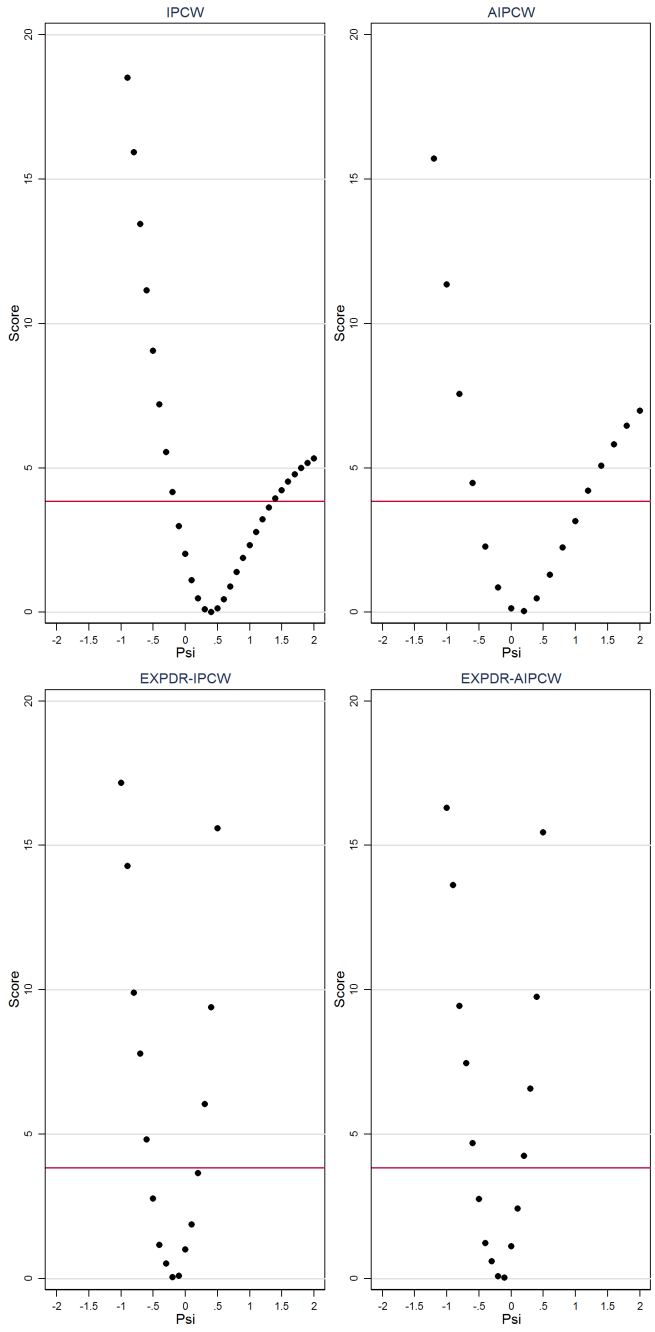


Figure 5.10: plot of Score statistic S versus candidate ψ values for the overall effect of Ventilator-associated pneumonia on mortality, IPC weight truncation [1p-99p]; IPC=Inverse probability of censoring.

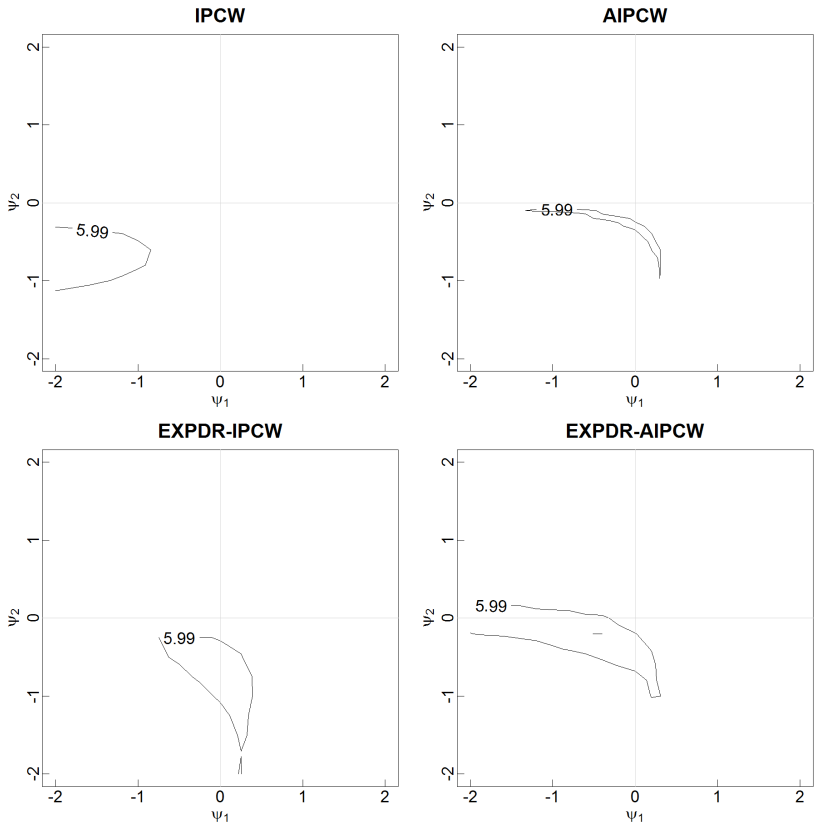


Figure 5.11: Contour plot of Score statistic S versus candidate ψ_1 and ψ_2 values for the joint effect of Ventilator-associated pneumonia (days 1-4 versus after 4th day of infection), IPC weight truncation [1]; IPC=Inverse probability of censoring.

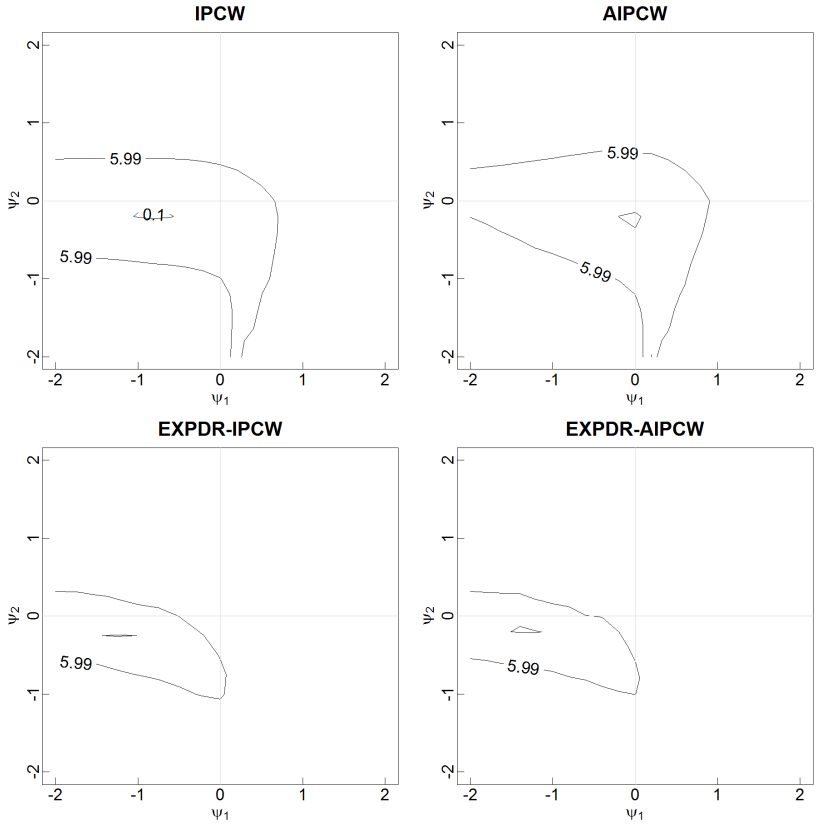


Figure 5.12: Contour plot of Score statistic S versus candidate ψ_1 and ψ_2 values for the joint effect of Ventilator-associated pneumonia (days 1-4 versus after 4th day of infection), IPC weight truncation [.2-5]; IPC=Inverse probability of censoring.

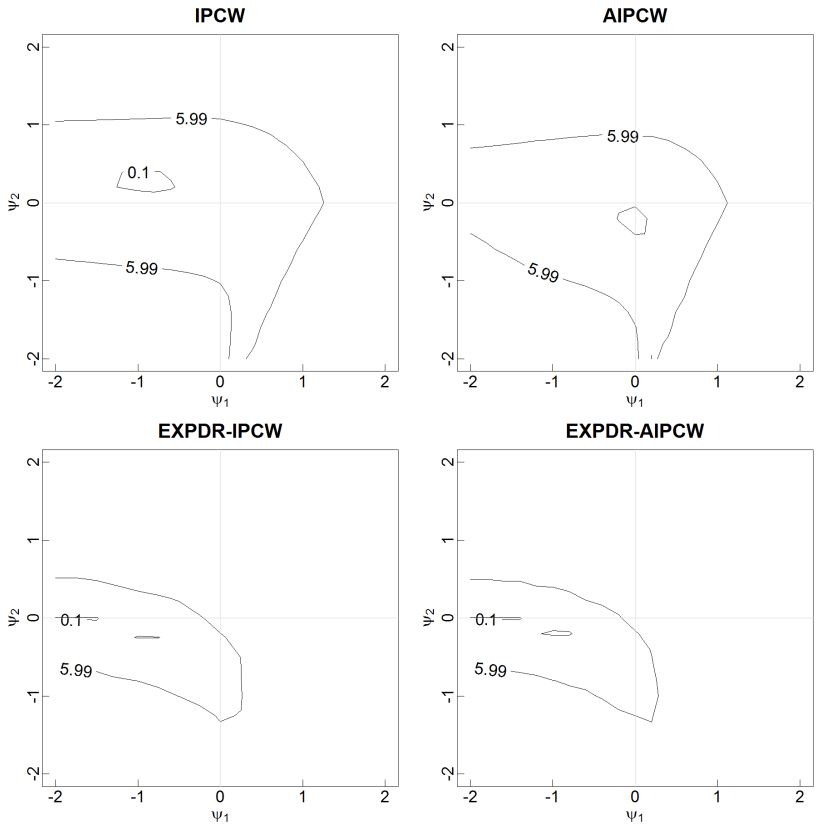


Figure 5.13: Contour plot of Score statistic S versus candidate ψ_1 and ψ_2 values for the joint effect of Ventilator-associated pneumonia (days 1-4 versus after 4th day of infection), IPC weight truncation [.1-10]; IPC=Inverse probability of censoring.

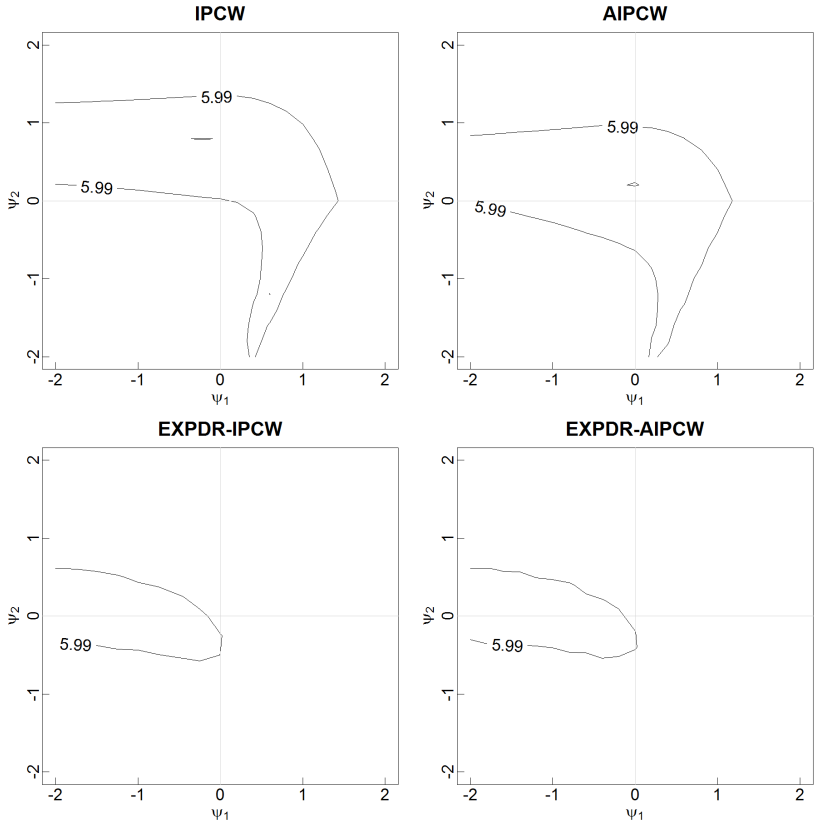


Figure 5.14: Contour plot of Score statistic S versus candidate ψ_1 and ψ_2 values for the joint effect of Ventilator-associated pneumonia (days 1-4 versus after 4th day of infection), IPC weight truncation 1-99 percentiles; IPC=Inverse probability of censoring.

CHAPTER 6

Concluding remarks

6.1 Summary of results

We used data from the *National surveillance of infections acquired in intensive care units (NSIH-ICU)* (see Chapter 2) to estimate the attributable mortality of Healthcare-associated infection (HAI). Particularly in the intensive care literature, the analysis of this effect gives controversial results. This controversy was confirmed when using standard stratification-based methods for confounder adjustment (such as cross-sectional logistic regression or time-dependent proportional hazards regression) to estimate this effect, with estimated attributable mortality effects that ranged from being protective to risk increasing depending on the statistical method that was applied on the same data.

A major problem with standard methods is their difficulty on how to adjust properly for confounding of the relation between the time-dependent variable "exposure to HAI" and the outcome variable "mortality". This is particularly challenging in the presence of time-dependent prognostic variables that act as cause

and effect of exposure at different time points. In the Introduction (Chapter 1), we give an overview of the key facts that show why standard stratification-based methods may give a biased estimate of the joint or aggregate causal attributable mortality effect whether or not regression adjustment is made for such variables, and this due to time-dependent confounding of the exposure-outcome relationship. Another problem is the difficulty of how to account for subjects that drop out of the study before the end of follow-up time. In our study, this comes in the form of Intensive care unit (ICU) patients that are being discharged alive from the unit, and therefore have a survival time outcome that is unobserved or censored. When the reason for such drop-out is linked to prognostic factors that also affect survival time, this will lead to selection bias. We then showed how estimators from causal inference, such as *Inverse probability weighting under Marginal structural models* and *G-estimation under Structural nested models*, can avoid the aforementioned issues and deliver estimates with causal interpretation.

In a first stage, we opted for the use of *Inverse probability of exposure and censoring weighted (IPECW) estimation under a Marginal structural proportional hazards model (MSPHM)* (Chapter 3). However, the strong association of certain prognostic factors with censoring coupled with the multitude of time-points lead to very low estimates of the cumulative probability of remaining under follow-up, resulting in extremely high Inverse probability of censoring (IPC) weights for certain patients. Truncation of these weights was thus needed, with the resulting causal effect estimate being possibly biased.

To resolve this, we developed two estimators of joint causal effects that allow for less dependence on (extreme) IPC weights. In the first, *IPECW estimation under a Marginal structural proportional hazards model for partial exposure regimes (MSPHM-P)* (Chapter 4), we analysed attributable mortality at discharge from the hospital, which is a less sensitive study outcome compared to mortality at discharge from the unit. We also used a regime defined by "being exposed to infection while remaining in the unit" that involves multiplication of inverse probability weights over less subject days, and therefore poses a smaller risk of these weights becoming too influential.

The second estimator that we proposed, *Augmented Inverse probability of cen-*

soring weighted (A-IPCW) G-estimation under Structural nested accelerated failure time model (SNFTM) (Chapter 5) avoids the use of inverse probability of exposure weights, and also yields estimates of the attributable effect that remain unbiased under misspecification of either the model for the censoring mechanism or either a model for the full data. This last property of doubly-robustness then allows to ignore IPC weighting completely, for example by setting IPC weights to 1 for all patients. Of equal importance is that the A-IPCW G-estimator provides improved efficiency compared to the standard Inverse probability of censoring weighted (IPCW) G-estimator, and this because it is able to use data from all patients instead of only those with observed or administratively censored survival time.

The proposed estimators are used in the analysis of the attributable effect on mortality of three types of ICU-acquired infections: ICU-acquired pneumonia, Ventilator-associated pneumonia (VAP), and Bloodstream infection (BSI), using historical multicentric data from the NSIH-ICU program (Chapters 3,4,5).

The proposed estimators are certainly worthwhile in their features of providing effect estimates with causal interpretation (IPECW, IPCW and A-IPCW estimators) and with the property of being doubly-robust and/or having improved efficiency (A-IPCW G-estimator under a SNFTM); however their application to the case study at hand did not entirely resolve the issues surrounding extreme IPC weights. For estimation under a MSPHM-P, the combined inverse probabilities for exposure and for remaining uncensored still lead to influential values to such extent that only regimes up to a certain time-point could be studied. For the A-IPCW G-estimator, full data modelling became increasingly difficult when IPC weights were set to 1. In the next Section, we explain how censored data can lead to both extreme IPC weights as well as difficulties in full data modelling. Therefore, the research for this problem does not stop here, and in what follows we give an overview of topics that we think warrant further investigation.

6.2 Further research

6.2.1 Inverse weighting versus augmentation to adjust for non-ignorable censoring

As previously mentioned, for IPCW estimators under both the MSPHM and the SNFTM, the estimated IPC weights had to be truncated in order for these estimators to converge. The group of subjects with extreme weights was more restricted when estimating under a SNFTM as compared to a MSPHM, because the standard G-estimator only uses observations from subjects with observed survival time or complete follow-up, which is a very selective group of subjects within the complete group. This has lead us to propose an A-IPCW G-estimator for the parameters of a SNFTM, which guarantees unbiased estimation of these parameters that is doubly-robust against misspecification of either a model for censoring or a model for the full data. We hereby followed Tan (2007)'s reasoning that the logical way in which Inverse probability weighted (IPW) estimators are further improved is by reducing the bias and/or variance of the estimates of their parameters. While our study is novel in that we connected G-estimation with augmented estimation, recent literature on doubly-robust estimation has shown that further improvements in efficiency are still possible. Indeed, while doubly-robust IPW estimators may behave well under correct specification of both working models, they lose this property when at least one of these models is misspecified (Kang and Schafer, 2007). Vansteelandt (2012) showed that the standard IPW estimator can be very sensitive towards misspecification of the propensity scores model in regions of prognostic factors L with very low overlap of the variable for which confounding with the outcome is to be resolved (in our case censoring), meaning those subjects or their time-point contributions with propensity score close to 0 or 1, and that such bias will be hardly resolved in a doubly-robust IPW estimator with minor misspecification of the outcome regression model. Vansteelandt and Joffe (2014) also demonstrated that such "extreme" propensity scores will lead to inflated variance of both the standard and the doubly-robust IPW estimator, and therefore to imprecise estimates. With these issues in mind, recent years have seen new versions of

doubly-robust IPW estimators with the specific objective of minimising bias and/or variance when one or both working models have been misspecified (Bang and Robins, 2005; Robins et al., 2007; Tan, 2007, 2008; Cao et al., 2009; Tsiatis et al., 2011; van der Laan and Rose, 2011; Rotnitzky et al., 2012; Vermeulen and Vansteelandt, 2014). The simulation experiments of these studies specifically demonstrate good behavior in the presence of extreme and influential inverse probability weights. As many estimators proposed in this study rely on IPW, with those of Chapters 3 and 5 specifically relying on truncated IPC weights, which can be seen as deliberate misspecification of the propensity score model, these estimators are therefore victim to the issues mentioned above. A future strategy is therefore to verify what recent techniques for doubly-robust IPW estimators could offer to data with extreme IPC weights under many time-points (such as ours).

Next to the development of the A-IPCW G-estimator, we elaborated on other strategies to cope with extreme IPC weights in Chapter 5 on SNFTMs. One strategy builds on the observation that the A-IPCW G-estimator yields its best results in terms of precision when IPC weights were set to 1, and this both in the simulation study as the application. Furthermore, the simulation study showed that this low precision could be accompanied with unbiasedness of the causal effect through careful construction of the full data model. In the context of our case study where we were forced to truncate (and deliberately misspecify) IPC weights in order for the G-estimation to converge, a valid approach might therefore be to abandon IPC weighting and direct all attention to full data modelling. Because the IPECW estimator under a MSPHM used in Chapter 3 also relied on (truncated) IPC weights and equally suffered from inflated variance, it would be worthwhile to develop an A-IPCW estimator under a MSPHM that would allow setting IPC weights to 1 in the same way as for the A-IPCW G-estimator. The augmentation algorithm under a MSPHM will likely differ from the one used under the SNFTM, unless the MSPHM's estimating equation is restricted to subjects with observed or administratively censored survival time.

Continuing with the scenario where IPC weights were set to 1, we experienced in our case study many problems in achieving convergence of particular versions of the A-IPCW G-estimator. This was due to strong correlation of the exposure

event with the outcome in the group of subjects with observed outcome. Let us hypothesise that, at a particular study time-point t, very limited overlap exists in the joint distribution of $(\overline{L}_t,\overline{A}_t)$ between censored and uncensored subjects. In an IPCW estimator, this can lead to $C_t = 1$ (censoring) being set almost deterministically for particular strata formed by $(\overline{L}_t,\overline{A}_t)$. This will result in very low probabilities for non-censoring and in extreme weights, to an extent that these need to be truncated in order to achieve convergence of the estimator. Therefore, for the IPCW estimator, the issue will be *non-positivity* of the conditional probability of remaining uncensored. In a full data augmentation procedure, due to particular strata containing little info on censoring at t, it might be difficult to correctly postulate a model for the mean full data outcome for non-censored subject days, which results in lack of fit and high residuals for these subject-days. The inverse is possible as well, with a good fitting full data model for non-censored subject days that however gives bad predictions for censored subject days. Such problems can then be exacerbated during augmentation over censored subjects and recursively over all time-points. The result of this is an estimating function with high variance of individual contributions and/or difficulties to reach a meaningful minimum for its average. Therefore, for the augmented estimator, the issue will be *extrapolation*, or the full data model needing to extrapolate its predictions over particular covariate regions made up by the distribution of $(\overline{L}_t,\overline{A}_t)$ with very low overlap between $C_t = 0$ and $C_t = 1$. In this light, the problems with the A-IPCW G-estimator under IPC weights set to 1 might seem expected, especially because we performed augmentation on the same data that lead to extreme IPC weights in the first place.

A future research strategy would be to investigate the possible common reasons for non-positivity and extrapolation, as well as remedies for these issues. In the setting of inverse probability of exposure weighting, Kurth et al. (2005); Crump et al. (2009) suggest to remove from the analysis those subjects with low propensity of exposure, the rationale being that these represent a particular subgroup of patients for which it is unrealistic (based on subject matter) to formulate a counterfactual or population outcome. However, applying such reasoning to subgroups with high propensity for being censored will be problematic if the factors that lead to such high propensity are not clearly defined. Furthermore, when A and L are

time-dependent, it will be equally problematic to base exclusions of observations on strata formed by $(\overline{A}_t, \overline{L}_t)$. To illustrate this, consider again causal Directed acyclic graph (DAG) 1.7 of Chapter 1 that represents the data after applying IPECW. Now consider the situation where we remove from the data particular strata of L_2 and A_2 due to these giving extreme IPC weights. Stratification on L_2 will then generate time-dependent confounding and bias of the causal effect of A_1 on Y_2, while stratification on A_2 might lead to impossible estimation of the effect of A_2 on Y_2. For these reasons, removing particular strata can only proceed if it strictly relies on baseline variables. One practical solution to resolve non-positivity would be to lower the study follow-up period T_m, as we did in Chapter 3 where we applied MSPHMs.

It is important to note that the censoring event in our study marks the time-point when a patient is discharged alive from the ICU. The link with a subject's underlying health status is therefore clearly established, to the extent that $C_t = 1$ marks the time-point where the patient is no longer in need of intensive care. This way, it is not difficult to think of possible reasons for violation of positivity and the corresponding need for extrapolation, for example by imagining that healthy patients would be discharged while unhealthy patients need to remain in the ICU. The IPCW and A-IPCW estimators work under the Ignorable censoring assumption (ICA), meaning that ($\overline{L}_t$,$\overline{A}_t$), the measured covariate history up to t, is sufficient to predict censoring at t, without residual association with future survival. The effect of a violation of this assumption due to omitting a particular prognostic factor can be studied as follows (Vanderweele et al., 2008). Let exposure A have a protective effect on censoring C ($A = 1$ leads to $C = 0$) and a harmful effect on outcome Y ($A = 1$ leads to $Y = 1$). Let ICA be violated by an unknown common prognostic factor U that causes censoring and outcome in the same way as exposure ($U = 1$ leads to $C = 0$ and to $Y = 1$). Restricting the analysis to subjects under follow-up ($C = 0$) will then create a non-causal association between A and U because in this subgroup $A = 0$ ($U = 0$) will be associated with $U = 1$ ($A = 1$), therefore creating a negative relationship between A and U and as consequence a protective effect of A on Y. The common cause U of C and Y can be seen as C being negatively associated with Y, collider-stratification on C therefore creates the

path $A \rightarrow U \rightarrow Y$, with negative effect on the first and a positive effect on the second arrow. Applying this reasoning to our case study, the protective causal effects of HAI on mortality we have found can be seen in light of such violation of ICA. It is therefore a valid strategy to obtain supplementary measurements on time-dependent prognostic factors to bring more predictive power in censoring risk. If these factors have overlapping distributions over censored and uncensored subjects, this might resolve the issues with respect to non-positivity as well.

6.2.2 Avoiding the ignorable censoring assumption

Given the comments of the previous Section, a valid strategy would be to investigate methods for causal effect estimation that avoid ICA. The use of models for the *subdistribution hazard* (Fine and Gray, 1999; Beyersmann and Schumacher, 2008) falls in such strategy. In this so-called "competing risk" approach, the survival time T now signifies the time-point t at which a subject experiences either the outcome event $(Y_t = 1)$ or the censoring event $(C_t = 1)$, these two now being called *competing events* because they compete for first occurrence within each subject. Using this approach and keeping with a discrete-time setup, the *cause-specific hazard of the outcome event Y* is defined as:

$$\lambda_Y^{\text{cs}}(t) = P(Y_t = 1 | Y_{t-1} = 0 \text{ and } C_{t-1} = 0) \tag{6.1}$$

while the *subdistribution hazard of the outcome event* Y is of the form:

$$\lambda_Y^{\text{sd}}(t) = P(Y_t = 1 | Y_{t-1} = 0 \text{ or } C_{t-1} = 1) \tag{6.2}$$

Because the subdistribution hazard $\lambda_Y^{\text{sd}}(t)$ conditions on $(Y_{t-1} = 0 \text{ or } C_{t-1} = 1)$, it will keep subjects in the risk set after censoring, without any possibility of experiencing the outcome event, and unlike the cause-specific hazard $\lambda_Y^{\text{cs}}(t)$ that uses as risk set those subjects under actual follow-up $(Y_{t-1} = 0 \text{ and } C_{t-1} = 0)$. Competing risk methods avoid the need for ICA: censored subjects remain in the risk set, they do not experience the outcome event, so no assumptions are stated with respect to the risk for outcome relative to subjects that were not censored.

As a consequence, there will be no need to make use of IPC weighting or full data augmentation to adjust for non-ignorable censoring. A competing risk analysis is therefore less ambitious in the results that it delivers, by strictly focusing on the outcome event at a patient's end of follow-up, which might be due to censoring. This is in relative contrast to an IPCW or A-IPCW estimator, which tries to reconstruct or create an ICU population not being discharged alive. Models for the subdistribution hazard have seen frequent use in studies of attributable mortality of HAI (Wolkewitz et al., 2009). They suffer from the same problems as standard stratification-based regression methods however, by not taking into account time-dependent confounding by prognostic variables affected by exposure, and as such their parameters have no causal interpretation. Bekaert et al. (2009) developed and applied a subdistribution hazard model for counterfactual outcomes, while Naimi and Tchetgen Tchetgen (2015) proposed the use of subdistribution hazard models within the parametric G-formula, both with the objective of obtaining estimators with causal interpretation.

A strategy that avoids any adjustment for non-ignorable censoring would consist in following all subjects until their length of follow-up reaches the administrative censoring time. In the context of our study, this would mean that data has to be collected on subjects after these were discharged alive from the ICU. However, many issues will arise when doing so; first, while the actual surveillance study is straightforward in its practical organisation by only demanding efforts from ICU staff, this will most certainly involve other partners when patients are followed after discharge from the unit. Second, the fact that censoring will be limited to a fixed end of follow-up date will not avoid the need for adjustment of the crude mortality effect of infection for time-dependent prognostic factors. These factors will likely differ when a patient is followed inside versus outside the ICU, the method therefore will need to take into account these different environments during which adjustment needs to take place. A possibility is to ignore any adjustment post ICU-discharge, similar to what we did in Chapter 4 were we analysed hospital attributable mortality effects.

6.2.3 G-Estimation under a structural nested failure time model

Because a SNFTM directly models the survival time, the administrative censoring time will need to be recalculated for each candidate value of the causal parameter in the G-estimation procedure, leading to possible administrative re-censoring of the counterfactual survival time. This can lead to information loss for the different candidate parameters, due to mapping observed survival times into administratively re-censored counterfactual survival times. As a consequence, irreguralities will be created in the estimating function for ψ, a phenomenon which is actually cited as one of the main issues preventing the adaptation of SNFTMs on a larger scale (Joffe et al., 2012). Structural nested cumulative hazard models (Young et al., 2009; Martinussen et al., 2011; Picciotto et al., 2012) offer a solution for this problem, in that they avoid re-censoring by modelling the failure indicator at each time-point. However, these are not without problems either, such as the risk of the counterfactual outcome exceeding the logical boundaries of the binary outcome.

In Chapter 5, we proposed an *Exposure risk doubly-robust (EXPDR)-IPCW G-estimator*, that offers robustness against misspecification of the model for exposure, but that also yielded better efficiency as compared to the standard IPCW G-estimator. In future research, one could focus fully on the properties of this particular estimator, and its added value relative to the standard (non robust) G-estimator that uses $g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\} = \Delta_{t,0}(\psi)$ (the counterfactual administrative re-censoring indicator). This last estimator is unstudied as well, as our standard G-estimator was based on $X_{t,0}(\psi)$, the counterfactual administrative re-censored survival time. For the EXPDR G-estimator, it would also be interesting to study the feasibility of obtaining a correctly specified proportional hazards model for $\Delta_{t,0}(\psi)$, particularly in scenarios where the model for the onset of exposure is misspecified. Additionally, we can study a direct analogue of our proposed EXPDR G-estimator for the standard G-estimator based on $X_{t,0}(\psi)$, for example by letting $g_t\{X_{t,0}(\psi), \Delta_{t,0}(\psi), \overline{L}_t\} = X_{t,0}(\psi) - E[X_{t,0}(\psi)|\overline{L}_t, Y_{t-1} = C_T = 0]$, with $E[X_{t,0}(\psi)|\overline{L}_t, Y_{t-1} = C_T = 0]$ postulating a linear regression model for the re-censored counterfactual survival time. We expect this last estimator to bring improvements in speed, which is particularly a problem of the actual EXPDR G-

estimator as it includes the estimation of a hazard model within the G-estimation procedure.

Speed is particularly an issue with our proposed A-IPCW and/or EXPDR G-estimators, because these incorporate the estimation of the parameters of at least one working model within the G-estimation procedure. It would be interesting to verify the properties of these estimators under naive versions of estimated working models, for example for a fixed value of the candidate causal parameter ψ. While this approach would lose the property of doubly-robustness, it may keep the improvements in efficiency as compared to the standard IPCW G-estimator.

6.2.4 Avoiding the sequential randomisation assumption

The imbalances of exposed and unexposed patient groups with respect to prognostic variables and the need to rely on the Sequential randomisation assumption (SRA) can be avoided when choosing randomised experiments as (alternative) study type. Such experiments study groups of patients that are randomised for particular intervention strategies for the prevention of HAI. Their primary outcome is mostly onset of infection, but other outcomes such as mortality are considered as well. A randomised experiment will offer more realistic estimates of the effect of prevention strategies on the reduction of infection incidence and its effect on mortality and morbidity, as compared to observational surveillance studies where mortality effects are estimated by comparing groups of patients with and without infection, therefore (unrealistically) hypothesising about all infections being prevented (Klompas, 2010; Umscheid et al., 2011). However, the drawback of such experiments is that, while designed properly for (already low) anticipated incidence rates for particular types of infection, designing these studies for detecting differences in (the even lower) attributable mortality will lead to infeasibly high numbers of patients to randomise. This renders the estimation of the attributable mortality effect of preventive measures of HAI by means of randomised experiments only practical when done by meta-analysis (Melsen et al., 2013). Also, the calculated attributable mortality needs to be interpreted in light of the actual intervention(s) that were studied, making it difficult to extrapolate findings of such studies for

policy measures.

Data from randomised experiments can be used for the estimation of the attributable mortality of infection, however such analysis will equally suffer from imbalances with respect to prognostic variables. In this case this is due to infection status being collected post-randomisation and therefore associated with outcome through common unmeasured prognostic variables. In such study design, and under the assumption that the intervention will only affect the outcome through infection, a technique such as *Instrumental variable analysis* (Greenland, 2000) is needed. However, such analysis estimates the effect of exposure by verifying how the risk of outcome changes when exposure would be avoided, therefore suffering from the similar drawback of using a counterfactual mortality outcome where all infections are prevented.

6.2.5 Variance estimation

This work mainly focused on unbiased estimators for the joint causal effect of time-dependent exposures, and by doing so neglected somewhat the issues on how to estimate the variance or confidence interval of the proposed estimators. This is however important, because even an estimator with the promise of being unbiased will be of limited use when the estimate of its confidence interval is too high. The estimators that we used rely on the estimation of nuisance parameters indexing working models for inverse probability of censoring and/or exposure weights (for IPECW and IPCW estimators), and a working model for the full data (A-IPCW G-estimator). Estimation of the variance of the causal parameter of these estimators will need to account for the uncertainty of nuisance parameters, failure to do so will lead to a conservative estimate of the asymptotic variance (van der Laan and Robins, 2003; Tsiatis, 2006). Furthermore, in the case of an IPCW estimator for causal parameter ψ that is doubly-robust under either a working model for IPC weights indexed by ϕ or a full data model indexed by ξ (such as the A-IPCW G-estimator), correct estimation of ξ (ϕ) will yield an estimator of the asymptotic variance of $\hat{\psi}$ that does not depend on the estimation of ϕ (ξ) being accounted for (Tsiatis, 2006; Vermeulen and Vansteelandt, 2014). In Chapter 5 on SNFTMs, we accounted for

estimation of all nuisance parameters except for those of the full data model. In a next step, it would be interesting to implement this, together with verifying whether the aforementioned property of the estimated asymptotic variance being insensitive towards accounting for estimation of nuisance parameters is also feasible for the EXPDR G-estimator that we proposed.

In Chapter 5, we accounted for estimation of nuisance parameters by supplementing the estimating function for the causal parameter with those of the nuisance parameters, and then obtaining a 95% Confidence interval (CI) by inversion of the score test. An alternative is an estimator of the asymptotic variance based on the sandwich method [see equation (1.83) in Chapter 1], but this has the additional difficulty that the matrix of partial derivatives of the estimating function with respect to the estimated parameters needs to be obtained, either analytically or numerically. The bootstrap procedure (Wasserman, 2004) is also an alternative, but can be tedious if it needs to include estimation of all working models.

6.2.6 Differences in effect estimates

Our study presents estimates for the causal effect of HAI on mortality using estimators under three models: a MSPHM, a MSPHM-P, and a SNFTM. These three models all give different results for this effect, we discuss briefly the possible reasons for this. First, MSPHMs and SNFTMs produce parameter contrasts between different types of counterfactual outcomes, and therefore lead to different interpretations. The SNFTM maps at each time-point the observed into the exposure-free survival time within subgroups formed by exposure A_t and prognostic factors L_t, therefore producing conditional contrasts. The MSPHM on the other hand, produces parameter estimates of population contrasts that are unconditional or strictly conditional on baseline variables, meaning that it calculates the hazard for the entire population being exposed, even when this would be unrealistic in practice. Due to the different effect types and to the non-collapsibility of conditional effects in nonlinear models (Hernàn et al., 2011), it is problematic to directly compare estimates from SNFTM and MSPHM modelling approaches on the same

data. The following approaches might enhance comparability. One can compare the predicted counterfactuals of both models that do have realistic interpretation, in our case this would be the survival times under absence of exposure. Related to this, is Chevrier et al. (2012)'s approach to fit a proportional hazard model on the counterfactuals produced by the SNFTM, to obtain causal parameter estimates in the form of hazard ratios. In the context of a point treatment study, Sato and Matsuyama (2003) explain a modification of the inverse probability weights under a marginal structural model that leads to conditional (instead of population) estimates. Hernàn et al. (2005) describe a way to convert the causal survival time ratio as estimated by a SNFTM into a causal hazard ratio. Also, Robins et al. (1994) describe an approach to derive population contrasts from SNFTMs using a technique called "blipping up", which was recently adopted by Picciotto et al. (2012) under a Structural nested cumulative failure time model.

Next to this, we list other reasons that help explain the found differences in effect estimates. The studies on MSPHMs and MSPHM-Ps looked at the effect of ICU-acquired pneumonia, while the study using SNFTMs looked at the effect of Ventilator-associated pneumonia, which is a subgroup of the former group. We studied ICU mortality as outcome in the studies on MSPHMs and SNFTMs, while this was hospital mortality in the study on MSPHM-P. Also, different datasets were used, with national multicentric data used for the MSPHMs and SNFTMs (however from different time-periods), while data from one center was used for the MSPHM-P. Estimation under all three models suffered from extreme IPC weights, but we handled this issue in different ways in the three studies. For the study on the MSPHM, we truncated weights starting at the subject day that these exceeded a certain value, a strategy which was also followed in the study using a SNFTMs but repeated for a number of truncation ranges. This study also presented an analysis that allowed IPC weights being set to 1. On the other hand, the study on the MSPHM-P avoided extreme IPC weights by limiting the number of days within its exposure regimes. Our hypothesis is that this last analysis feature might have the most impact on the differences between the results of the three studies, more specifically on the reason why the study using the MSPHM-P presents a harmful effect while the other two present slightly protective towards neutral effects. The

studies using the MSPHMs and the SNFTMs also demonstrate a harmful effect of infection on mortality late after infection onset, which is in agreement with the harmful effect found by the MSPHM-Ps if we would assume that this estimate is driven by mortality occurring late after infection onset.

6.2.7 Interpreting and using effect estimates

Given the protective and neutral attributable mortality effects that we found for ICU-acquired pneumonia and/or VAP, it would be problematic to conclude that prevention for these types of HAI is not needed any more. Next to investigating the effects of infection on morbidity outcomes (see the next section), these results also call for verifying whether the case definition of the studied infection type is sufficiently specific. It is worth noting for example that the majority of ICU-acquired pneumonia (and therefore also of VAP that are declared in the NSIH-ICU program are diagnosed using so-called "semi-or non-quantitative" techniques, which are know to be much less specific than quantitative techniques for pneumonia detection (Fagon et al., 1993; Chastre et al., 2003). A future strategy might therefore exist in defining subgroups of infection (based on diagnostic strategy for example) that give higher risks for mortality, and investigate the attributable mortality for these specific subgroups. Such knowledge can then form a basis for possible fine-tuning of case definitions used for standardised surveillance.

6.2.8 Analysing morbidity

While this study focused on estimators for the attributable effect of HAI on mortality, it would also be of interest to look at effects on morbidity parameters, such as Length of stay (LOS) within the unit or hospital, or use of medical treatment. Consider the estimation of the attributable effect of HAI on morbidity outcome "discharge alive from the ICU". Such analysis will aim to estimate the extra LOS that HAI-patients need to recover from HAI, as compared to uninfected patients. To estimate this effect, we will need to adjust carefully for all available time-independent and -dependent confounders for the HAI-LOS association, and secondly we need

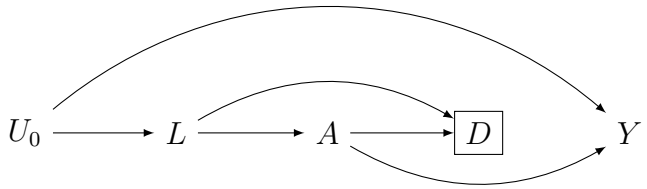


Figure 6.1: Causal directed acyclic graph depicting non-causal association between exposure (A) and the morbidity outcome (Y) through the mortality event (D).

to separate the effect on mortality from the one on discharge alive from the ICU. Analysing time to discharge from the ICU, and using LOS of both survivors as well as non-survivors to do so, will be problematic. This is because LOS can be the result of different pathways that patients can follow in response to HAI, for example with infection leading to death (discharge alive) being due to absence (presence) of appropriate treatment. This means that the analysis will be challenged by mortality acting as a competing event for the morbidity outcome, in the remaining paragraphs we demonstrate this further and outline eventual estimation strategies.

As an example, we consider a study with a single time point $T_m = 1$. We assume the causal DAG of Figure 6.1, with variables U_0, A, L as explained before, and variables D and Y now representing the mortality and morbidity (for example "discharge alive from the unit") events respectively. Causal DAG (6.1) shows a "survivors-only" analysis in which D is surrounded by a box, indicating that the analysis selects on observations with $D = 0$. In such analysis, non-causal paths $A \rightarrow \boxed{D} \leftarrow L \rightarrow Y$ and $A \rightarrow \boxed{D} \leftarrow L \leftarrow U \rightarrow Y$ will be opened through collider-stratification on D. Stratification on variable L to block these paths then leads to a stratified model for the risk of morbidity Y, for example $P(Y = 1|a, L, D = 0; \beta^{\mathrm{m}})$ indexed by unknown parameter β^{m}. Now consider the counterfactual outcomes Y_a and D_a, or the outcomes that would be observed if exposure level $A = a$ would be assigned instead of the observed exposure level. Note that we do not consider the counterfactual $Y_{(a,d=0)}$, or the morbidity outcome when assigning exposure level $A = a$ and when keeping the subject alive ($d = 0$), because we consider the event D to be non-intervenable. By this, for the two outcomes Y and D combined,

define the set of counterfactual outcomes $(Y_a, Y_{1-a}, D_a, D_{1-a})$.

Using the aforementioned stratified model for the risk of morbidity outcome Y, we attempt to formulate a causal contrast that compares the risk of morbidity across exposed and unexposed subjects as follows:

$$\begin{aligned} \frac{P(Y=1|A=1,L,D=0;\beta^{\mathrm{m}})}{P(Y=1|A=0,L,D=0;\beta^{\mathrm{m}})} &= \frac{P(Y_1=1|A=1,L,D_1=0;\beta^{\mathrm{m}})}{P(Y_0=1|A=0,L,D_0=0;\beta^{\mathrm{m}})} \\ &= \frac{P(Y_1=1|L,D_1=0;\beta^{\mathrm{m}})}{P(Y_0=1|L,D_0=0;\beta^{\mathrm{m}})} \end{aligned} \tag{6.3}$$

in which the first equality is due to the consistency assumption, and the second due to SRA (modified to include conditioning on $D_a = 0$). Contrast (6.3) cannot be considered as a causal contrast. This is because the numerator and denominator of (6.3) are defined within different subgroups, being based on $D_1 = 0$ and $D_0 = 0$ respectively. To resolve this, we might be tempted to rely on ICA and remove the conditioning statement $D = 0$ from the expectations in contrast (6.3), as we did previously in the context of censoring due to discharge alive from the ICU. However, a typical censoring event leads to an unobserved outcome, while under a "dropout due to death" scheme, the outcome event is simply undefined. Use of ICA will be therefore invalid.

The morbidity event being undefined in a subject that drops out due to death is also the reason why contrast (6.3) is non-causal. To see this, in the numerator of this contrast, the subgroup $D_1 = 0$ will be a mixture of subjects having $(D_0 = 0, D_1 = 0)$ and subjects having $(D_0 = 1, D_1 = 0)$, or those subjects that will survive no matter what exposure level [hence called "always survivors (as)"] and those that will only survive when being unexposed (or where exposure protects against death) respectively. The denominator of (6.3) uses subgroup $D_0 = 0$, which is a mixture of subjects having $(D_0 = 0, D_0 = 0)$ and subjects having $(D_0 = 0, D_1 = 1)$, or the same "as" group as used for the numerator but now complemented with subjects that only survive when being exposed (or where exposure leads to death). We see now that the expectations in the numerator and denominator of contrast (6.3) both condition on subgroup "as", but that they differ in terms of their complementing subgroups. It is clear that a comparison of the risk of morbidity between groups

$(D_0 = 1, D_1 = 0)$ and $(D_0 = 0, D_1 = 1)$ is non-causal, because a subject of the former group can never be part of the latter group. Also, within each one of these subgroups, it will be impossible to validly compare the risk of morbidity, because it will be undefined due to death in one of the contrast's studied exposure levels.

Subgroups defined by counterfactual mortality outcomes under possible levels of exposure are called *Principal strata*. Following the above arguments, we will attempt to restrict the estimation of the causal contrast towards subgroup "as", which is called *Principal stratification* (Robins, 1986, Section 12.2; Frangakis and Rubin, 2002). Because we cannot identify from the observed data which subjects belong to this principal stratum, identifying assumptions will need to be formulated that allow calculating the causal contrast within this subgroup. Following this, and using a longitudinal study design, (Tchetgen Tchetgen, 2014) recently introduced *Survivor Marginal structural models*, which are described to estimate causal contrasts in individuals that would survive any exposure regime.

6.3 Final conclusion

When searching methods for the statistical estimation of the attributable effect of HAI on mortality, one needs to avoid (1) the time-dependent confounding by prognostic factors for mortality that can act as cause and effect of infection, and (2) the selection bias due to non-ignorable censoring and caused by only analysing data from subjects under follow-up within the ICU or hospital. Estimators from causal inference are able to correct for these issues. However, these are known to struggle with strong associations between the censoring event and particular time-dependent factors, including exposure to HAI. We proposed novel estimators of joint causal effects that (1) allow to use exposure regimes and study endpoints that are less sensitive towards non-ignorable censoring, and (2) provide robustness of the causal estimand towards misspecification of the model for censoring.

CHAPTER 7

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