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The true cost of epidemic and outbreak diseases in hospitals

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London, January 2018

ABSTRACT

Background: Outbreaks of infectious diseases may result in bed pressures, which are often mitigated by delaying new admissions due to beds being unavailable. This painfully illustrates to policy makers and the public what is meant by the economic notion of “opportunity costs”: The value of the next-best alternative forgone, or in this situation: The value of the beds for the displaced patients. These opportunity costs need to be captured adequately in economic analyses.

Methods: Suitable approaches for estimating the opportunity costs of healthcare beds from the perspective of health-maximising decision makers were searched for in a literature review. Lack of adequate methods drove the development of a novel approach. Differences among approaches were explored using, as a case study, hospitalisations for norovirus-associated gastroenteritis. Its hospital burden was quantified nationally for England using statistical modelling. Afterwards, a stochastic mathematical model of hospital wards was built to explore the additional bed pressures on occupancy levels due to transmission-dynamic norovirus outbreaks.

Results: Health-maximising decision makers should approximate the opportunity costs of healthcare beds by considering the net benefit of the second-best admissions forgone. This novel approach estimated a loss of 6,300 quality-adjusted life years (QALYs) annually in England and economic costs of £190–£298 million due to norovirus, roughly 2–3 times higher than the financial expenditures incurred of £108 million. During norovirus outbreaks, additional bed pressures arise 83.0% of the time, preventing a mean of 6.8 (range 0–44) new admissions that could have been admitted had there been no outbreak.

Conclusions: Owing to market imperfections, the true value of healthcare beds differs from the value calculated using pragmatic conventions. In this thesis, these opportunity costs were estimated for the first time by explicitly including the wider health impact for other patients awaiting admission. The higher values obtained may impact the outcome of economic analyses.

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LIST OF ABBREVIATIONS AND ACRONYMS

AU\$	Australian dollar	HCAI	healthcare-associated infection
CBA	cost-benefit analysis	HES	Hospital Episode Statistics
CC	Complication and Comorbidity	HNORS	Hospital Norovirus Outbreak Reporting System
CCI	Charlson comorbidity index	HPRU	Health Protection Research Unit
CEA	cost-effectiveness analysis	HRG	Healthcare Resource Group
CI	confidence interval	HTA	health technology assessment
CUA	cost-utility analysis	ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th revision
DALY	disability-adjusted life year	ICER	incremental cost-effectiveness ratio
DTaP	diphtheria, tetanus, and acellular pertussis	IDRN	Infectious Disease Research Network
D&V	diarrhoea and vomiting	IID	infectious intestinal disease
E. coli	Escherichia coli	IQR	interquartile range
Eq.	equation	JCVI	Joint Committee on Vaccination and Immunisation
EQ-5D	EuroQol five dimensions	LE	life expectancy
FCE	Finished Consultant Episode	LOCF	last observation carried forward
GBP (£)	Great Britain pound sterling	LOESS	locally weighted regression fit
GDP	gross domestic product	LOS	length of stay
GE	gastroenteritis	LSHTM	London School of Hygiene and Tropical Medicine
GII	norovirus genogroup II	LYG	life-year gained
GII.4	norovirus genogroup II, genotype 4	max	maximum
GHB	Gross Health Benefit	MCMC	Markov chain Monte Carlo
GMB	Gross Monetary Benefit	min	minimum
GP	general practitioner	MPB	marginal private benefit
HAI	hospital-acquired infection	MPC	marginal private costs

MSB	marginal social benefit	QALY	quality-adjusted life year
MSC	marginal social costs	R ₀	basic reproduction ratio
MSM	multi-state model	RCT	randomised controlled trial
n/a	not applicable	SD	standard deviation
NESSS	National Enhanced Surveillance System for <i>STEC</i>	SEIAR	susceptible-exposed-infectious-asymptomatic-recovered
NHB	net health benefit	SEIR	susceptible-exposed-infectious-recovered
NHS	National Health Service	SIR	susceptible-infectious-recovered
NICE	National Institute for Health and Care Excellence	SitReps	Situation Reports
NIHR	National Institute for Health Research	SGSS	Second Generation Surveillance System
NLM	National Library of Medicine	STEC	shiga toxin-producing <i>Escherichia coli</i>
NMB	net monetary benefit	TAH	total abdominal hysterectomy
NOCB	next observation carried backward	TC	total costs
NoV	norovirus	TLH	total laparoscopic hysterectomy
OC	opportunity costs	UCLH	University College London Hospital
OCR	occupancy rate of bed-days	UK	United Kingdom
ODE	ordinary differential equation	USA	United States of America
ONS	Office for National Statistics	US\$	United States dollar
PCR	polymerase chain reaction	VC	variable cost proportion
PHE	Public Health England	WHO	World Health Organization
pts	patients		
Q1	lower quartile		
Q3	upper quartile		

1 INTRODUCTION

“Economists, like doctors, are seeking to extend life and relieve misery. In the case of doctors, the premature mortality and the misery is due to disease. In the case of economists, it is due to scarcity. Health economics stands at the interface between those two important fields of human endeavour.”

Alan Williams, *Health and Economics*, 1987.^[1]

This chapter establishes terminology and provides concise background information and context on the economic and epidemiological contents of this thesis.

The true cost of infectious epidemic and outbreak diseases in hospital, and indeed in any healthcare setting, is not captured in expenditures alone.^[2] One needs to account for health impact on different patients in terms of mortality and morbidity, too. This makes epidemics and outbreaks costly not only in monetary terms but also in terms of loss of health.

In semi-enclosed settings like hospitals, infectious disease outbreaks easily lead to disruptions with infected inpatients staying longer and negative spill-over effects for other patients awaiting admission who cannot be treated due to beds being unavailable. As a result, hospitals and the healthcare system as a whole are negatively impacted financially, and patients may experience adverse health effects (including temporary or permanent decrements in health as well as fatal outcomes).^[3]

Estimations of the value of hospital beds should account for this alternative use forgone, that is, the use for other patients awaiting admission rather than the extended hospital stay of the current occupants, which is known in economics as the “opportunity cost”. More formally, opportunity costs can be defined as “the value of the forgone benefits because a resource is not available for its best alternative use”.^[4] In practice, however, the forgone benefits are rarely considered; instead, the market price and financial accounting expenditures of the chosen alternative are simply taken, assuming that the resources spent

could have been used for another alternative up to the same value. From an economics perspective, analysts thereby make the implicit assumption that the supply and demand of resources are in equilibrium.^[4,5]

Hospital beds, however, are not in market equilibrium as demonstrated by e.g. bed pressures and waiting lists (more on this later in section 1.1.1).^[6-8] This translates to an excess demand by patients for hospital beds that exceeds the supply of bed-days by the healthcare system (note: bed-days are a composite measure of the number of beds and the time they are occupied in terms of days). The disequilibrium means that the expenditure incurred does not approximate the value of the opportunity costs, unless this occurs purely by chance.^[5] Therefore, the current convention of costing bed-days based on market prices or financial expenditures is not adequately capturing the opportunity costs from the forgone patients.

In general, these opportunity costs for other patients only exist in situations where there is an excess demand of beds or a shortage of supply. Therefore, opportunity costs for other patients arise in settings with high rates of bed occupancy. This is the case in England, where acute care hospitals face very high bed occupancy levels above a mean of 90%,^[7] but occupancy rates are also high internationally.^[6] Patients who cannot be admitted due to beds being unavailable may therefore result in health and economic losses to the healthcare system and society on the whole.

The situation may get worse during infectious disease outbreaks, which may cause exogenous supply and demand shocks. During outbreaks, demand for beds increases temporarily due to the spread of infection, and infected inpatients stay longer than they would have without infection. Also, the supply of bed-days may decrease when beds and wards are closed precautionary for infection control, or healthcare staff is absent due to illness and cannot timely be replaced or their work compensated for by others.

Given the importance of bed-days for the healthcare system, and given the fact that they are a main cost-driver in economic analyses involving hospitalisation,^[4] it is important to address this gap between current methods and reality. As such, this thesis aimed to find a suitable approach of estimating the opportunity costs of bed-days by including the health impact for other patients, and quantifying the health and economic losses from unpredictable surges in bed demand for the healthcare system and society.

For illustration, norovirus infection in hospital was used as a case study of an infectious disease that leads to periodic bed pressures and is a recurring public health concern of hospitals in England, particularly during winter (more on norovirus is presented later in section 1.3). The cost of norovirus outbreaks is most likely being underestimated using currently prevailing costing approaches.

1.1 OPPORTUNITY COSTS AND HEALTH ECONOMICS

“The health administrator has usually equated ‘health economics’ with ‘money questions in the field of health.’ But, money is not the central problem of health economics. *Health economics is concerned with the optimum use of scarce economic resources for the care of the sick and the promotion of health, taking into account competing uses of these resources.* [Italics supplied] The basic problems are of two kinds: the organization of the medical market, and the net yield of investment in people for health.”

Selma Mushkin, *Toward a definition of health economics, 1958.*^[9]

In 1958, Selma Mushkin published one of the first definitions of health economics,¹ and she highlighted the idea of opportunity costs prominently.² The concept is widely regarded as fundamental for economics^{3, [5,14]} including the economic sub-discipline of health economics.^[4,9,21,22] They are most often referred to within the framework of reimbursement decision-making, particularly when using micro-economic evaluations of healthcare interventions. In order to guide reimbursement decisions, some jurisdictions

¹ The article of Selma Mushkin was published five years before the landmark publication of Kenneth Arrow in 1963,^[10] which is widely recognised as having founded health economics as an economic sub-discipline.^[11-13] For her definition, Mushkin adopted Lionel Robbins’s neo-classical notion of economics from 1932 that prevails until today: “Economics is the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses.”^[14: p.15]

² The concept was first named “alternative costs” by Friedrich von Wieser (who also coined the term “marginal utility”), and subsequently “Wieser’s law”, before the term “opportunity costs” prevailed.^[15] The ideas have been expressed by scholars for centuries—with less catchy terms—, including most notably Adam Smith (1776), Frédéric Bastiat (1850), Léon Walras (1874), Friedrich von Wieser (1884), and Vilfredo Pareto.^[5,16,17]

³ The notion of opportunity costs is one of the cornerstones of economics, alongside the scarcity of resources, the need to make choices, and the push for efficiency (i.e., producing the desired products, goods and services at the lowest possible expenditure).^[18-20]

like England have used incremental cost-effectiveness thresholds, which represent the value of a hypothetical second-best alternative displaced.^[23,24]

Most frequently, however, these principles are explicitly referred to when valuing resources for which no market price exists (e.g. time and informal care); a “shadow price” is then derived from the second-best alternative (e.g. paid employment).^[21: p.1552] For other resources, market prices and average accounting expenditures are conventionally considered to approximate the opportunity costs in practice.^[4]

“Although the theoretical proper price for a resource is its opportunity cost (that is, *the value of the forgone benefits because the resource is not available for its best alternative use*), [Italics supplied] the pragmatic approach to costing is to take existing market prices unless there is some particular reason to do otherwise (for example, the price of some resources may be subsidized by a third party such as a charitable institution).” — Drummond et al., 2005.^[4: p.57]

Importantly, the meaning of the term “costs” differs between accountants and economists. Accountants measure historical expenditures for financial planning and reporting;^[25] they are thus able to say what “costs” (i.e. expenditures) were incurred when a particular choice was pursued. Economists on the other hand focus on the costs of taking different courses of action, including the status quo (which may be to “do-nothing”). The economic perspective is thereby inherently linked to the concept of choice among mutually-exclusive options.^[5] In order to avoid ambiguity, this thesis will aim using the more accurate term “expenditures” when referring to accounting “costs”, and reserve the term “costs” to refer to the economic idea of opportunity costs.

In the next section, the standard microeconomic market model of supply and demand will be briefly reviewed in light of the theoretically proven tendency of prices to converge to opportunity costs for markets operating under the conditions of perfect competition.^[18] This background information will be used to establish the central critique within this thesis: the common practice of current costing conventions for pragmatic reasons. Only the key aspects of the standard microeconomic market model can be covered here; more details can be found elsewhere.^[18,19]

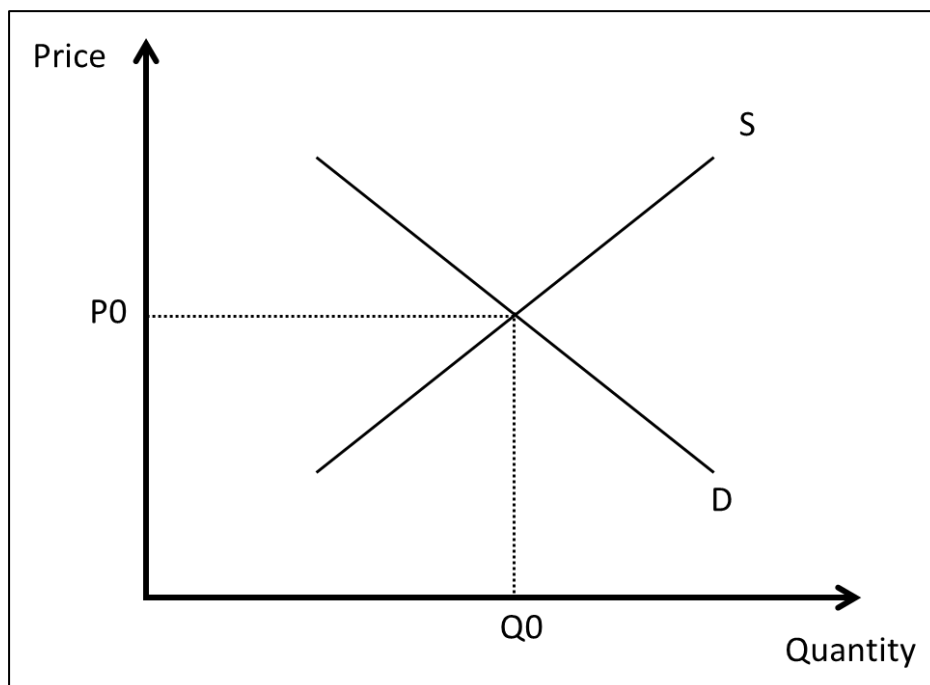
1.1.1 Microeconomic model of supply and demand in perfectly competitive markets

The microeconomic theory of supply and demand considers as benchmark the perfectly competitive market model, which is characterised by (at least) four conditions:

- I) many suppliers and demanders;
- II) perfect information for rational decision-making;
- III) free entry and exit to the market; and
- IV) identical products.^[18,26]

In such a perfectly competitive market, the model predicts that rational consumers will demand goods (or services like in healthcare markets) until the marginal benefit of each good (or service) equals the price to satisfy the consumers' self-interest (note: the concept of marginality refers to the change in costs/benefits when providing one additional unit).^[27] Likewise, producers will supply goods and services until the marginal costs of production for each unit is equal to the marginal revenue (i.e. the price) to maximise economic profits.^[18,26,28] These self-regulating forces of supply and demand will lead to the establishment of an economic equilibrium price with an associated quantity of goods (or services);^[18,29] see point P_0, Q_0 in Figure 1.

Figure 1. Microeconomic model of supply and demand in perfectly competitive markets



D: demand curve, P_0 : unit price at equilibrium point of supply and demand, Q_0 : quantity at equilibrium point of supply and demand, S: supply curve

This equilibrium price is equal to the “marginal opportunity costs”^[5] as it is “Pareto efficient”, i.e. at this point nobody can be made better off without making someone else worse off, which has also been called “the first optimality theorem of welfare economics”.^[10] Hence, there is no more-profitable alternative use of resources at the equilibrium point of supply and demand in perfectly competitive markets (see Figure 1). The market price would readily equal the marginal opportunity costs for both suppliers and demanders, and across resources.

However, the assumptions of a perfectly competitive market cannot be met in reality due to externalities and information asymmetries.^[30] The healthcare market is additionally characterised by market failures like:

- I) quasi-monopolies and quasi-monopsonies (i.e., few suppliers and collective demanders);
- II) moral hazard and supplier-induced excess demand (i.e., information asymmetries between patients and insurers, and care providers);
- III) barriers to freely enter and exit (e.g. due to patent-protection, professional licensing, first-mover advantages, high initial investment costs, and regulatory requirements); and
- IV) non-identical products and services (in part due to difficult, if not impossible, standardisation).^[10,26,31,32]

Moreover, consumers of healthcare (i.e., patients) frequently do not fully recognise the future benefit of interventions (for themselves and society) nor account for all external effects (positive and negative externalities) on third parties at the time of consumption,^[18,33] both of which hold particularly for infectious diseases. Due to these market imperfections, the price mechanism will likely result in disequilibrium, and hence the market price and expenditure poorly reflect the “true”⁴ costs of resources.

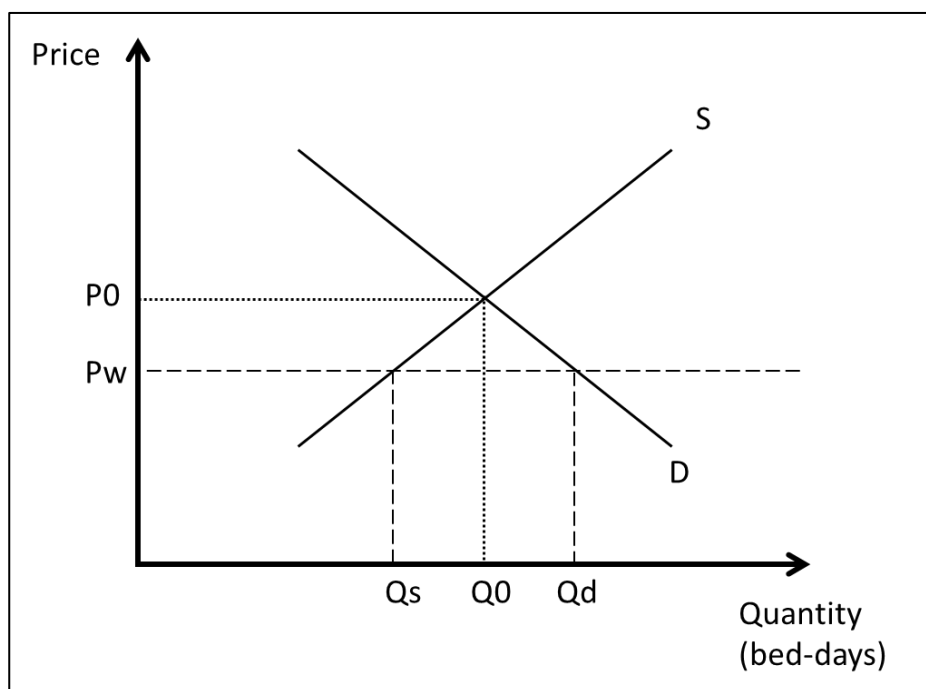
⁴ Note that the adjective “true” implies a normative valuation in terms of the opportunity costs, i.e. the “highest-valued” forgone alternative,^[34] making the terms “true value/costs”, “opportunity costs”, and “economic costs” essentially synonymous from an economic perspective. Nuances among “opportunity costs” and “economic costs” are explained in chapter 2, section 2.5.

1.1.2 Remarks on market failures for hospital bed-days

Although the market model of perfect competition has its limits, it still serves to illustrate three ideas about the marginal opportunity costs in cases of hospital outbreaks of an infectious disease (note: the following graphs merely serve for illustration and hence ignore for simplicity the known price-inelasticity of demand for non-elective care,^[35] which would result in nearly vertical slopes of the demand curves).

First, many hospitals need to operate with waiting lists due to a shortage of aggregate supply over aggregate demand for bed-days, at least in the National Health Service (NHS) in England.^[8] Hence, the current price level cannot be assumed to reflect full capacity^[36] as the service provision is in disequilibrium (to whatever degree; see for illustration the arbitrary price set at P_w in Figure 2, at which level the demand for bed-days, labelled with Q_d , exceeds the supply of bed-days, Q_s , by $Q_d - Q_s$).

Figure 2. Shortage due to demand exceeding supply (illustrating waiting lists)

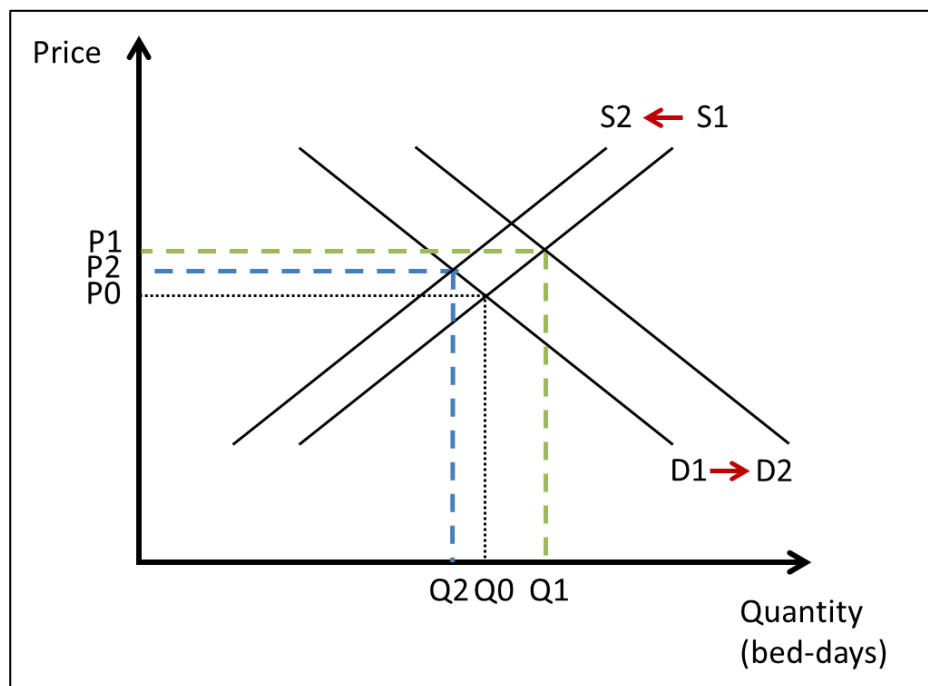


D: demand curve, P_0 : unit price at equilibrium point of supply and demand, Q_0 : quantity at equilibrium point of supply and demand, S: supply curve

Second, infectious epidemic and outbreak diseases may change the quantity of bed-days demanded and supplied temporarily (known as demand and supply shocks).^[18] The demand for bed-days increases due to infected patients being newly treated plus staying

longer, shifting the demand curve to the right (see curve D2 in Figure 3). Likewise, the supply for bed-days may decrease temporarily due to beds being isolated and blocked or healthcare personnel becoming infected and absent (or worse, an entire ward being closed). If this cannot be adjusted for (by e.g. putting patients on trolleys or escalation beds, or by buying beds from the private sector), the supply decreases, indicated by the curve S1 shifting to the left, indicating a lower quantity provided (curve S2 in Figure 3).

Figure 3. Demand (increase) and supply (decrease) shocks

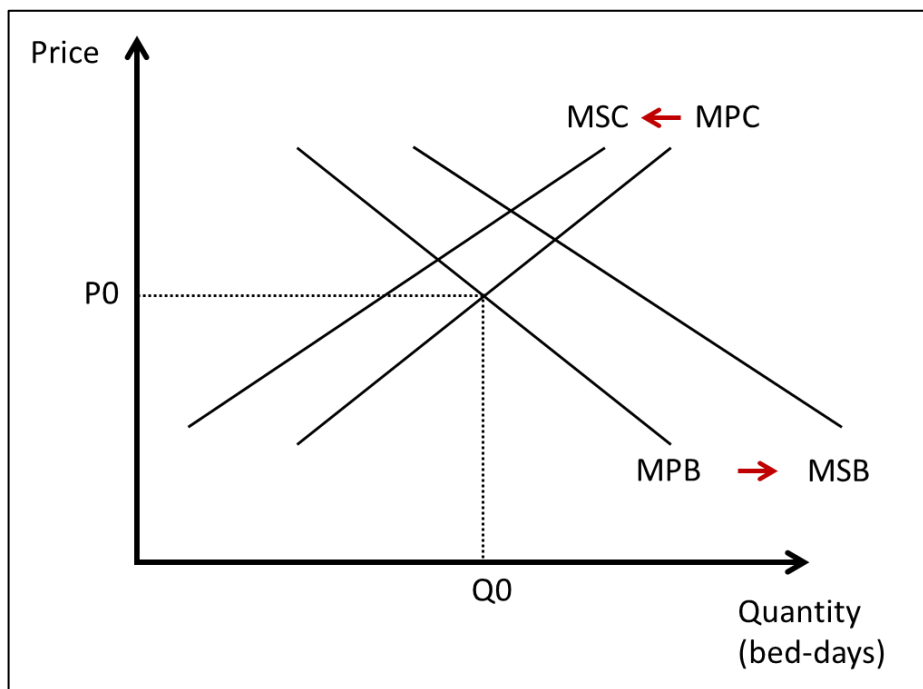


D: demand curve, P0: unit price at equilibrium point of supply and demand, Q0: quantity at equilibrium point of supply and demand, S: supply curve

Moreover, both shocks may occur simultaneously. In a competitive market, the price levels would change accordingly and it seems that irrespective of supply and/or demand shocks, the equilibrium price/marginal costs would be higher than before according to the microeconomic model (which would be difficult to quantify if not knowing the exact supply and demand functions). Again, the assumption of the market price equalling the opportunity costs does not hold. It seems hence desirable from the perspective of hospitals, society and patients to quickly regain access to these resources and keep the bed-day closure as well as length of the outbreak short (or avoid them altogether) to minimise the capacity loss for treating other patients.

Third, infections have considerable external effects for others that are not considered by the price mechanism. Positive externalities for society from preventing infections (e.g. herd immunity through high levels of vaccination)^[37] result in a higher marginal social benefit than the marginal private benefit of individuals (demanding vaccination; see curve MSB in Figure 4).^[18] Likewise, negative externalities for society associated with the preventable spread of an infection (e.g. ward closures impacting other patients outside the hospital awaiting admission) result in higher marginal social costs than the marginal private costs for hospitals (see curve MSC in Figure 4). For instance, hospitals may “overproduce” bed-days for cases who could have been prevented through vaccination (= “excess” stays).

Figure 4. Private versus social costs and benefits due to externalities



MSC: marginal social costs, MPC: marginal private costs, MSB: marginal social benefit, MPB: marginal private benefit, P_0 : unit price at equilibrium point of supply and demand, Q_0 : quantity at equilibrium point of supply and demand.

When taken together, these three market imperfections support the impression that in settings with an unmet, excess healthcare demand the “true” value, or shadow price, of bed-days will not converge to the financial expenditures. This follows from the imbalance of the supply and demand of bed-days, which do not reach the competitive market equilibrium, even in the long-run. Moreover, the three observations give reason to believe

that the economic costs of bed-days are likely to be higher than indicated by market prices or expenditures.

However, the health impact for patients who cannot be admitted due to beds being unavailable have not yet been explicitly considered. This theme is central to the thesis, and I explore this issue by exploiting the special situation of recurrently occurring epidemic and outbreak diseases in hospitals; see next section 1.2.

1.2 INFECTIOUS EPIDEMIC AND DISEASE OUTBREAKS

An “outbreak” of an infectious disease can loosely be described as the sudden local emergence of new (incident) cases linked to a geographically limited setting like a school, hospital, street or district, often due to a common source of exposure.^[38,39] Thereby, outbreaks are an escalation of an infrequent “sporadic” case through the occurrence of at least two cases linked in time and space by a common source.^[40,41]

An “epidemic” in turn describes the temporary increase in the incidence of a disease by more than what is naturally expected to occur in a more-widespread geographical area like the community or a region;^[38,39] cf. the Severe Acute Respiratory Syndrome (SARS) epidemic in 2002/2003 that started as an outbreak in Hong Kong,^[42,43] or the West-African Ebola virus epidemic in 2013–2016 that began as an outbreak in the border region of Guinea.^[44]

When an epidemic further escalates widely across continents it is described as a “pandemic”, which is a large-scale epidemic of a disease with common source and “widespread geographic extension”;^[45] cf. the 2009 H1N1 influenza virus pandemic.^[46,47] An “endemic” refers to the constant prevalence of a disease in a population or geographical region;^[38] such as viral gastroenteritis in the community.^[48,49]

The focus of this thesis will rest on epidemic and disease outbreaks of gastrointestinal illnesses, which form a prime example for the situation of supply and demand of healthcare beds being in disequilibrium. Moreover, outbreaks occur frequently, easily lead to disruptions in healthcare service provision and delivery, and the typically semi-enclosed nature of healthcare settings and the close proximity of patients worsen the situation.^[50,51] As such, the demand of bed-days regularly exceeds the supply during outbreaks due to longer staying inpatients and empty beds becoming unavailable for reasons of infection control (e.g. bay or ward closures to prevent further transmission).

From an economic perspective, outbreaks form a temporary exogenous shock in the short-run demand of bed-days as inpatients are likely to stay longer due to the infection than they otherwise would have without infection. In the long-run, the demand for bed-days would be expected to return to equilibrium. However, negative spill-over effects like cancelling elective procedures may occur for other patients awaiting admission, and their health might be negatively impacted as a direct result of the outbreak through transmission dynamics. These consequences would likely not have occurred had the outbreak been avoided.

This thesis will look specifically at hospitals of the NHS in England, which face recurring seasonal bed pressures in winter,^[52] particularly due to outbreaks of infectious intestinal diseases (IID). In other countries like the USA, these outbreaks are a more pressing concern in long-term care facilities rather than hospitals.^[53] Globally, the community burden is quite sizeable with an annual mortality of more than 1.3 million deaths (95% uncertainty interval, 95%-UI: 1.2–1.4 million),^[54] which is reflected in terms of the indirect costs of forgone productivity (typically measured with wage rates and time) of \$56.2 billion (95%-UI: \$40.9–\$78.3 billion) globally.^[55]

1.3 CASE STUDY: NOROVIRUS INFECTIONS IN HOSPITAL

Infection of norovirus-associated gastroenteritis greatly fits the purposes of this thesis. It recurrently causes hospital outbreaks and disruptive bed pressures, particularly in winter.^[52] Therefore, the supply and demand of hospital beds will not be in equilibrium (cf. section 1.1.1), and the financial expenditures incurred are unlikely to equal opportunity costs.

Moreover, there are inevitable negative externalities and knock-on effect for others, including patients, staff and the wider community.^[18] With demand for hospital care being high in England and mean occupancy rates above 90%,^[7] outbreaks of norovirus place additional pressures on an otherwise already burdened system. As such, there is a real impact on other patients' health, and economic losses occur for society.

Lastly, there is no anti-viral treatment or vaccine currently available yet.^[56,57] Other than monitoring patients and providing supportive therapies such as rehydration, there is not much a hospital can do for cases infected with norovirus, which is self-limiting and not requiring any special medical attention,^[58] with a comparatively low mortality^[58] and an

expected relatively low loss of quality-adjusted life years (QALYs). Furthermore, admitting infected individuals risks spreading the virus to other inpatients and causing outbreaks. Hence, Public Health England^[59] and the National Health Service (NHS) in England advise otherwise healthy individuals with gastrointestinal symptoms to avoid visiting their general practitioner (GP) and healthcare facilities like care homes or hospitals.^[60]

In the following sections, a brief overview of this pathogen is given on its clinical and epidemiological characteristics in general (section 1.3.1), the situation of outbreaks in healthcare settings with a focus on hospitals (section 1.3.3), the status quo of the research and development in treatments and vaccines (section 1.3.2), and the existing decision-analytical models (section 5.8.1).

1.3.1 Clinical and epidemiological characteristics of norovirus

One of the first accounts of gastroenteritis being caused by a non-bacterial pathogen came from the paediatrician John Zahorsky who published in 1929 an article entitled “Hyperemesis hiemis or the winter vomiting disease”.^[61,62: p.668] It took until 1972 to clearly attribute a gastroenteritis outbreak in Norwalk, Ohio, USA in 1968 to a positive-sense, single-stranded RNA virus for the first time, giving “norovirus”⁵ its name.^[62,66]

The *Norwalk virus* is the only species of the genus called *Norovirus* from the *Caliciviridae* family of viruses.^[67] Six genogroups have been identified for *Norovirus*, with the genogroups GI, GII and GIV infecting humans.^[64] The genogroups are further subdivided into genotypes based on mutations in the amino acid sequence of the capsid, i.e. the shell of a virus made of protein.^[64] The specific capsid is the primary immunogenic component of the virus and drives the immune response.^[58]

The predominant human genotype has been GII.4 since 1995.^[63] Since then, a new GII.4 strain has emerged about every two to four years and replaced the previous variant in

⁵ Other, previous names for norovirus include “small round-structured viruses”, “gastric flu”, and “winter vomiting bug/disease”.^[63,64] In the International Statistical Classification of Diseases and Related Health Problems, ICD-10, the *Norwalk virus* is coded in chapter I (“Certain infectious and parasitic diseases”) under block A08 “Viral and other specified intestinal infections” as A08.1 “Acute gastroenteropathy due to Norwalk agent, Small round structured virus enteritis”.^[65]

response to population immunity (with the seven variants so far being Grimsby-US1995/1996, Farmington Hills-2002, Hunter-2004, Yerseke-2006a, Den Haag-2006b, New Orleans-2009, Sydney-2012).^[58,64] Although recent reports indicate that a new GII.17 genotype has emerged in parts of Asia and Australia,^[68,69] the Sydney-2012-like GII.4 strain remains to be the most commonly detected one in England in laboratory reports and outbreaks.^[70,71]

Norovirus is highly contagious; ingestion of small doses of 18–1000 viral particles suffices for an infection.^[58,72] Thereby, the average risk of infection is higher for norovirus than for any other virus.^[72] The viral particles are also able to survive for some time *ex vivo* on surfaces,^[58] with one report describing two workers getting infected after removing a previously dry-vacuumed carpet 12 days after a norovirus outbreak in a hospital ward.^[73] Norovirus also resists low levels of chlorine disinfection and temperatures between 0–60 °C.^[58] When analysing the sequential spread via fingers in four replicate experiments, it was shown that fingertips contaminated with faecal samples of norovirus would always transfer the virus to the first four clean typical surfaces (i.e., taps, door handles, and telephones), and in one replicate experiment even up to seven surfaces.^[74]

The primary mode of transmission is the oral-faecal route via direct person-to-person contact. However, transmission is also possible via contaminated food, water, environment, or aerosolized particles.^[58,67]

A dose-dependent incubation period of 0.5–2.0 days precedes the development of typical symptoms of acute gastroenteritis, including the characteristic projectile vomiting and diarrhoea, but also abdominal pain, headaches and fever.^[58,75,76] Infected persons already shed the virus during this pre-symptomatic period,^[77] but with lower levels of transmission than during the symptomatic period.^[78,79] Moreover, about 20–30% of infected patients remain asymptomatic after incubating the virus, yet they can be potentially infectious.^[58,80] In a study of 170 oyster- and food handler-associated outbreaks in Japan from April 2001 to January 2005, it was hypothesised that the norovirus GII.4 strain leads to more asymptomatic infections than other norovirus genotypes given its comparatively lower attack rate (median 41% vs. 56.9%).^[81]

In those patients who develop symptoms after incubation, they usually last for 0.5–2.5 days in the healthy population,^[40,75] for whom this infection is self-limiting and does not

require any special medical attention.^[58] In England, such individuals are therefore advised to “avoid visiting GP surgeries, care homes, and hospitals if they have symptoms” by Public Health England^[59] and the NHS.^[60] On the other hand, vulnerable populations like young children, elderly and immunocompromised patients, who are frequently affected by hospital outbreaks of norovirus,^[40,58,82] may experience symptoms lasting between 2–5 days,^[40,67,83] partly due to it taking them longer to clear the virus and partly due to worsening existing conditions.^[58] Chronic norovirus infections are rare but do occur particularly in the immunocompromised,^[84,85] and they are a concern for being natural reservoirs of the virus with the potential for developing new variants that evolve through an accumulation of mutations.^[86]

After experiencing symptoms, the virus can still be shed for some time in another asymptomatic period,^[78,79] which is why there is the general recommendation for staying at home for 48 hours after gastrointestinal symptoms resolved.^[87]

The mechanisms and extent of immunity to norovirus are not well understood.^[53,79] About 20% of individuals in Europe are genetically resistant to infection and symptoms of the GII.4 norovirus strain through a mutation that disables the 1,2-fucosyltransferase (FUT2) gene (known as “non-secretors” or “secretor-negative”).^[88] However, some of the genetically susceptible “secretors” or “secretor-positive” individuals have also been shown to be immune, leading to overall immunity levels in challenge studies of between 30% and 45%.^[79,89] Moreover, the duration of immunity will impact the role of future vaccines as a longer-lasting immunity will reduce the need for re-vaccinations. Acquired immunity was long thought to last from six months up to two years based on challenge/re-challenge volunteer studies in the 1970s and 1990s,^[90,91] while a recent modelling study estimated that temporary immunity may last for up to 8.7 (95%-CI: 6.8–11.3) years.^[79]

Lastly, mortality associated with viral gastroenteritis in high-income countries is mostly an issue in healthcare settings and affecting the elderly.^[58] In England and Wales, death certificates recorded by the Office for National Statistics (ONS) registered a mean (and identical median) number of 35 (range: 23–48) norovirus-associated deaths between 2010 and 2016, where norovirus was classified as the underlying cause based on ICD-10 code A08.1.^[92] One study investigated 43 deaths (24 in hospitals and 19 in elderly-care facilities) in 38 outbreaks in England and Wales between 1992 and 2000, which resulted in a case-fatality rate of 7.5/10,000 and mean deaths per outbreak of 0.07 (range: 0–2).^[93] A comprehensive regression analysis of national data from hospitals and the community

in England and Wales between 2001 and 2006 found that, on average, approximately 80 deaths of patients aged ≥ 65 years were associated with norovirus each year.^[94]

1.3.2 Treatment and vaccine development to prevent norovirus-infection in humans

As of early-2018, no antiviral treatment or vaccine for norovirus is available.^[56,57] The main reason for the delay has been the inability to culture norovirus *in vitro* in the past,^[95] which is why most vaccine candidates have been based on virus-like particles (VLPs). Only recently in 2013 was the human norovirus successfully replicated in a small-animal (mouse) model,^[96] and in 2016 a way was found to grow the virus *ex vivo* on the basis of using human stem cells.^[97] These developments may impact future research and development efforts.

Development of antiviral treatments have concentrated on monoclonal antibodies as well as interferons.^[98] Most of these efforts have not reached (advanced) clinical trials yet.^[57,98] For vaccines, there are already at least five vaccine-candidates in development,^[56] with all but two undergoing pre-clinical trials as of early-2018. The pharmaceutical company Vaxart is currently developing a monovalent GI.1 vaccine based on an adenoviral-vector, which is undergoing phase I clinical trials.^[99] The most advanced vaccine-candidate is being developed by the pharmaceutical company Takeda Vaccines, which further developed a monovalent GI.1 vaccine^[100] into a bivalent GI.1/GII.4 vaccine^[101,102] that is currently in a phase IIb efficacy trial in healthy adults (due to be completed in February 2019).^[103] The corresponding phase I-II vaccine efficacy challenge study with 50 vaccinees and 48 placebo controls was unable to show that the vaccine-candidate significantly reduced the number of cases, with 27 infections among vaccinees and 30 among controls, $P=.420$, and 13 symptomatic cases among vaccinees and 16 among controls, $P=.509$ (note: the study included only genetically susceptible secretor-positive individuals).^[104] However, the vaccine-candidate was able to reduce the severity of the vomiting and/or diarrhoea of any degree by 52% (95%-CI: 8.3–74.9%; $P=.028$), of moderate-to-severe disease by 68% (95%-CI: -11.2–90.8%; $P=.068$) and severe disease by 100% ($P=.054$).^[104]

1.3.3 Outbreaks of norovirus in hospitals

“The introduction of SRSVs [*author’s note: small round-structured viruses, one of the previous names for norovirus*] into hospitals is inevitable since these infections lack a defined prodrome, the onset of symptoms is usually sudden and they commonly circulate widely in the community”.^[105: p.499] Hence, “[...] attempts to circumvent their introduction into hospitals are unrealistic”.^[106: p.1241]

E. Owen Caul, *J Hosp Infect*, 1994,^[105: p.499] **and *The Lancet*, 1995.**^[106: p.1241]

Norovirus causes more than 90% of viral gastroenteritis and 50% (range: 36–59%) of all-cause gastroenteritis outbreaks based on a review of six studies from different European countries.^[67] Norovirus outbreaks occur frequently in (semi-)enclosed settings like hospitals and long-term care facilities, but also in prisons, hotels, schools/universities, restaurants, cruise ships, military camps, and private homes.^[58,93] Thus, any infection in the community may potentially impact healthcare settings too, and vice versa, through being admitted as a patient, a visitor or staff working there.^[86]

Surveillance data in England and Wales between 1992 and 2000 showed that person-to-person contact was the primary mode of transmission in 85.2% of 1,877 norovirus outbreaks across settings, and in 95.0% of outbreaks in hospital (716 of 754 in total; 1.3% were foodborne and 3.7% other/unknown).^[93] Another study showed that transmission of the virus from one patient in hospital to another took on average 1.86 days.^[50,58]

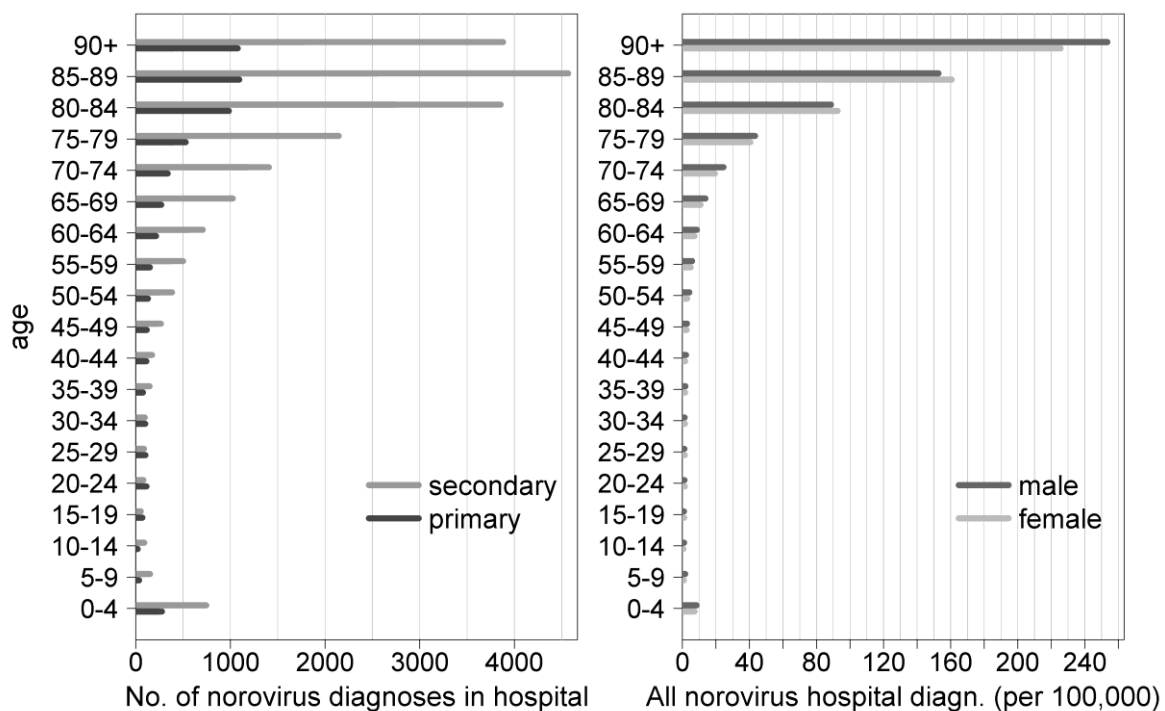
Norovirus outbreaks are commonly identified through the occurrence of at least two cases (among patients or hospital staff) in a hospital functional care unit (e.g. a ward) that either experience similar symptoms due to an illness (excluding personal circumstances, incontinence and laxative drugs) or have a laboratory-confirmed infection.^[40,41] Cases also need to be linked in time, ranging in different studies between two and seven days.^[41,50,51,107,108]

Norovirus outbreaks occur throughout the year but they peak during the winter between September to March.^[109] The potential influence of environmental (e.g. temperature) and host behavioural factors on norovirus and its seasonality are not yet fully understood.^[63] Figures from 1,877 reported norovirus outbreaks in England and Wales between 1992–2000 showed that 754 outbreaks (40.2%) occurred in acute care hospitals, with another 724 (38.6%) in long-term care facilities.^[93]

Typically, between 80–90% of hospital outbreaks in England result in ward or bay closures.^[110] For the epidemiological season running from July 2014 to June 2015, 808 (94%) of the 858 hospital outbreaks of norovirus in England led to ward/bay closures or restrictions to admissions.^[111]

For all hospitals of the NHS in England, the Hospital Episode Statistics (HES) database holds the records of patients. Between April 2009 to March 2016, a total number of 43,735 cases were diagnosed with norovirus,⁶ which is the equivalent of 11.6/100,000 people in England using end-year population estimates.^[113] Of these, 9,635 (22%) cases had a primary norovirus diagnosis and 34,100 (78%) had a secondary norovirus diagnoses, with a clear increase in secondary diagnoses by age (i.e., above 50 years old; Figure 5).

Figure 5. Age-stratified number of hospital diagnoses of norovirus (ICD-10: A08.1) in England, mid-2009 to mid-2016. Left: primary or secondary diagnosis; right: sex.



⁶ These statistics are based on the ICD-10 code A08.1, “Acute gastroenteropathy due to Norwalk agent, Small round structured virus enteritis”^[65], and Finished Consultant Episodes (FCEs): One FCE “is a continuous period of admitted patient care under one consultant [*note: a consultant is a senior physician or surgeon in hospital with completed specialist training and overall responsibility for patient care*] within one healthcare provider. FCEs do not represent the number of [*individual*] in-patients, as a person may have more than one period of care within the year”^[112].

Moreover, when separating these cases by age and sex and standardising per 100,000 people in England,^[113] most hospital cases were recorded in the elderly population above 60 years of age, with a dramatic increase in the number of cases above the age of 90 years of up to 253.44 cases per 100,000 males and 225.57 cases per 100,000 females (Figure 5). The difference in sex is negligible for most age groups except for the very old population above 90 years of age (Figure 5). The reasons for the difference in this age group are unclear, and they cannot be explained by a generally higher proportion of men being admitted than women above 90 years of age as the opposite is true.^[114]

In general, the quality of the hospital diagnosis coding can be questioned due to A) miscoding norovirus as another form of gastroenteritis e.g. in the absence of laboratory confirmation, potentially even as a non-infectious intestinal disease,^[115,116] and B) coding practices of secondary diagnoses being known to vary between data providers.^[117] Moreover, previous studies on rotavirus vaccination have reported that of all gastroenteritis diagnoses more than 70% across ages (and more than 80% in children aged <5 years) were coded as “unspecified viral intestinal infection” (ICD-10 code A08.4) or as “diarrhoea and gastroenteritis of presumed infectious origin” (A09).^[118,119] Hence, other techniques for estimating the hospital burden of norovirus in England are necessary to yield more accurate estimates.

1.4 RESEARCH AIMS AND QUESTIONS

This thesis explores the true value of bed-days, in particular during epidemic and disease outbreaks in hospital. For illustration, the ideas are applied to patients with norovirus.

The guiding research questions are as follows:

1. How should the value of the resource “bed-days” be calculated during epidemic and disease outbreaks in hospital, i.e. temporary supply and demand shocks?
2. What is the hospital burden of disease for norovirus in England using different approaches to estimating bed-day costs, including those addressed in research question 1?
3. What is the impact of norovirus outbreaks in hospital on bed pressures and occupancy levels of wards in England?

Research question 1 addresses the methodological part of this thesis, while research questions 2 and 3 apply the new methodology to norovirus outbreaks in hospital.

1.5 OUTLINE OF THE THESIS

In order to answer the research questions in this thesis, I integrate a qualitative literature review with statistical, mathematical and economic modelling techniques.

Research question 1 is explored by means of a scoping literature review of the different approaches used to estimate the value of the opportunity costs of resources in general, and of bed-days in particular (chapter 2). In the absence of an adequate existing approach from the perspective of a decision maker who aims to maximise population health, I also propose a novel approach for estimating the value of bed-days.

Answering research question 2 has required numerous steps. First, the number of bed-days lost due to cases with acute gastroenteritis during winter is estimated by imputing non-randomly missing values for weekends and the Christmas period (chapter 3). Of particular interest here are the bed-days kept unoccupied for infection control, which are used for a comparison with the voluntary hospital outbreak surveillance data at Public Health England (chapter 4). The compulsory nature of the data collection allows for a comprehensive overview of the impact of acute gastroenteritis on bed pressures nationwide during winters (chapter 3).

Second, a previously developed backward stepwise regression model^[115,116] is applied to hospital episodes of gastroenteritis and various enteric pathogens to estimate the current norovirus-attributable national hospital burden (chapter 4). For an accurate representation of the resources used, the excess length of stay due to norovirus is estimated with a multi-state model for inpatients admitted for a different primary diagnosis than gastroenteritis (chapter 4).

Third, the economic burden is quantified for the second-best admissions forgone. In order to use the novel approach for valuing opportunity costs, I modelled the forgone health gain from hospitalisation in terms of “quality-adjusted life years”, QALYs, which are a composite measure of “time” in terms of life years lived and the “quality” of that time (chapter 4).^[120,121] Afterwards, the methods in research question 1 are used to cost the bed-days conventionally, and with the novel approach (chapter 4).

Answering research question 3 involves building a transmission-dynamic compartmental model in order to simulate norovirus outbreaks in hospital. The model is nested within another mathematical model of typical hospital wards of the NHS in England with stochastic admissions and discharges to obtain bed occupancy levels at the

baseline without norovirus outbreaks (chapter 5). This model is then used to explore the daily risk of an inpatient becoming infected with norovirus for hospital wards per year, and the impact of norovirus outbreaks on bed pressures using the number of longer staying inpatients and the number of patients that would have been admitted had there not been any outbreak.

Lastly, chapter 6 provides a general discussion and conclusion of the entire body of research presented in this thesis.

2 HOW TO ESTIMATE THE VALUE OF BED-DAYS

This chapter expands on the concepts presented in the introductory chapter 1, section 1.1, of how to adequately estimate (i.e., measure and value) costs from an economic perspective. The paper presented in this chapter begins with a historical outline of how opportunity costs have been estimated in the past for resources in general. Afterwards, the focus rests on bed-days given that they are one of the major cost factors of any economic analysis involving hospitalisation.

The various applications for bed-days show how researchers have been using different estimation techniques to derive different results. A novel approach is developed that builds on the economic theory and the practical applications.

Title of paper, name of authors and affiliations:

Estimating the opportunity costs of bed-days.

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2.1 COVER SHEET OF RESEARCH PAPER 1

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Student	Frank Sandmann
Principal Supervisor	Prof. Mark Jit
Thesis Title	The true cost of epidemic and outbreak diseases in hospitals

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Health Economics		
When was the work published?	06.11.2017		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed and undertook the literature review, extracted the data, analysed and interpreted the findings, developed the novel approach, and drafted the paper and subsequent revisions during the peer-review. JVR, SRD, WJE, and MJ equally provided critical comments on the design of the literature review, the analysis and interpretation of findings, the novel approach,
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	and the different versions of the paper. All authors contributed to conceiving the study. I presented a poster of this study at the Health Economics Study Group (HESG) Winter 2016 Conference (Manchester, 2016) and the LSHTM Poster Day (London, 2016), and I was invited to give a seminar at the Health Economics Research Centre of the University of Oxford (Oxford, 2016).
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Student Signature:  _____ **Date:** 27.01.2018

Supervisor Signature:  _____ **Date:** 27.01.2018

2.2 ABSTRACT

Opportunity costs of bed-days are fundamental to understanding the value of healthcare systems. They greatly influence burden of disease estimations and economic evaluations involving stays in healthcare facilities. However, different estimation techniques employ assumptions that differ crucially in whether to consider the value of the second-best alternative use forgone, of any available alternative use, or the value of the actually chosen alternative.

Informed by economic theory, this paper provides a taxonomic framework of methodologies for estimating the opportunity costs of resources. This taxonomy is then applied to bed-days by classifying existing approaches accordingly. Differences in valuation between approaches and the perspective adopted will be highlighted, and the framework will be used to appraise the assumptions and biases underlying the standard approaches that have been widely adopted mostly unquestioned in the past, such as the conventional use of reference costs and administrative accounting data.

Drawing on these findings, a novel approach is presented for estimating the opportunity costs of bed-days in terms of health forgone for the second-best patient, but expressed monetarily. This alternative approach effectively re-connects to the concept of choice and explicitly considers net benefits. It is broadly applicable across settings and for other resources besides bed-days.

2.3 INTRODUCTION

In healthcare settings, resources like personnel and beds are scarce. Hence, choosing to treat or care for one patient means a lost opportunity to treat or care for another patient in the presence of an unmet demand, as exemplified by waiting lists. It is such a trade-off that loosely embodies the economic notion of “opportunity costs”.

Most economic textbooks define opportunity costs similar to “the value of the next-best alternative” forgone, while others consider “(the value of) what is given up”.^[122, p.10,123, p.7] Although comparable, the second phrase lacks an explicit valuation ranking,^[34] i.e. it is not clear whether to take the value of the second-best alternative use, of any available alternative use, or of the actually chosen use. Moreover, the understanding of “costs” also differs between disciplines, with economists focusing on choosing between different possible courses of action given limited resources, and accountants focusing on recovering historical expenditures for financial planning and reporting.^[25] For economists, only factors relating to a sacrifice from making a particular decision are relevant “pain costs” (i.e., costs “felt” by the decision maker), while factors not associated with a sacrifice from that decision are irrelevant “sunk costs”.^[5] This is most obvious for factors fixed in time due to contractual obligations, which cannot be significantly reduced in the short-term, with variable cost factors becoming the sacrifice of a choice to be made.

Major health economic textbooks endorse valuing opportunity costs with the second-best alternative forgone,^[4,18,124] particularly for resources without a market price. A “shadow price” is then derived to represent the “true social value (or opportunity cost) of non-marketed resources, such as time and informal care”.^[125, p.1552] For marketable resources, however, the market price, reference costs and average accounting expenditure of the *chosen* alternative are conventionally considered to approximate the opportunity costs for pragmatic reasons.^[4] Explicit consideration of the second-best alternative is hence dropped and although common practice, this is only adequate under the idealistic market conditions of perfect competition.^[5,36]

Given the well-known market failures in healthcare,^[10,126] this paper scrutinises the estimation techniques that have been adopted in the past mostly without questioning the underlying assumptions and biases. Healthcare beds may be considered as prime example of an imperfectly-marketed resource whose opportunity costs may in fact diverge from the values calculated using conventional methods, not least because hospitals are

multiproduct firms with a complex production function in which different units may operate internally as individual profit centres. Bed-days are also a highly influential cost component of any analysis involving stays in healthcare facilities.^[4] Therefore, it was investigated in this paper how to adequately estimate the economic value of bed-days, with a special focus on decision-making agents aiming to maximise health.

The paper is structured as follows: The methods and sources are outlined next. In the results a general taxonomy is compiled of methodologies for estimating the opportunity costs of resources. Then, the focus turns on the resource “bed-day” and co-existing approaches are presented that were classified according to the taxonomy. To distinguish the theoretical methodologies for resources from the practical applications for bed-days the terms “methodology” and “approach” were used, respectively. The approaches were illustrated and appraised before proposing a novel alternative. The proposal and paper are then discussed before offering concluding remarks.

2.4 METHODS

First, theoretical methodologies of estimating opportunity costs were categorised in a taxonomy based on (reviews of) economic textbooks ^[4,34,122,123,127,128] as well as James Buchanan’s treatise on the concept’s origins up to the late 1960s and diverging views among orthodox (neo-classical) and heterodox (subjectivist) schools of economics.^[5]

Second, existing applications for the valuation of bed-days were identified through a scoping review of the health and economics literature. Relevant articles were initially searched for up to 28th November 2014 in two bibliographic databases: PubMed (NLM) and EconLit (Ovid). Additionally, the reference lists of all articles screened in full-text were subsequently checked for relevance. The search was last updated on 02nd December 2016, using the following search terms: “bed day” AND (costs OR demand* OR valu*); “opportunity costs” AND (“bed day” OR health* OR hospital*); for details of the syntax see Table 4 in the Appendix (section 2.9). All articles were included that directly applied an approach to estimate the opportunity costs of bed-days or one suitable for bed-days. Records were excluded that did not entail any approach of estimation or any suitable approach for bed-days; were not written in English; or did not include a full-text article. Articles using wage rates were also excluded although their relevance to this work is discussed later and the general idea of multiplying time with a monetary value is

incorporated in one of the approaches. The identified applications in the articles were then generalised and clustered into different approaches, which in turn were classified according to the taxonomic framework.

Third, the different approaches were compared and appraised to explore their impact on bed-day values. Drawing on these findings, a novel approach was developed for valuing the opportunity costs of bed-days in line with economic theory and from the perspective of a decision maker aiming to maximise health with limited resources.

2.5 RESULTS

2.5.1 General taxonomy of methodologies to estimate the opportunity costs of resources

Early economic theorists initially interpreted opportunity costs in terms of units of a displaced alternative product: “If among a nation of hunters [...] it usually costs twice the labour [time] to kill a beaver which it costs to kill a deer, one beaver should naturally exchange for or be worth two deer”.^[17] In this simplified example, hunting deer is the second-best alternative for the hunters, and the relative costs of production reflect the true opportunity costs of the hunters’ labour time.^[5]

Departing from natural units was seen as necessary by economists to account for the monetary value used in almost all kinds of exchange.^[5,14] Opportunity costs should then be represented by the net benefit (i.e., benefit minus expenditure; also called the natural or accounting profit) to account for different benefits and expenditures associated with alternative options.^[34,127] The second-highest net benefit, i.e. the second-best alternative to choose, constitutes the true opportunity costs,^[122,123] with all other alternatives comprising trade-off costs.^[34] Moreover, the opportunity costs should not be confused with the economic profit, which is the difference of the highest and second-highest net benefits.^[34]

For reasons of practicality, orthodox neo-classical economists then moved to an interpretation of the value of the displaced product being approximated by the expenditure on the alternative chosen. Its costs of production are assumed to reflect the value of a forgone alternative that could have been produced had the same amount of money been spent on it instead.^[4,5] This interpretation is valid for perfectly competitive markets as

there will be no alternative, more profitable use of resources at the equilibrium price of supply and demand (i.e., it is “Pareto efficient”; see the first optimality theorem of welfare economics).^[18] It is thus a special situation where the values of all alternatives converge, making net benefits irrelevant in the absence of profitable alternatives as their benefits equal their expenditures.

Due to externalities and information asymmetries, most markets fail to reach the competitive equilibrium,^[30] including healthcare.^[10] Expenditures will then not readily reflect opportunity costs as profits/losses indicate a better use of resources existing elsewhere. Thus in case the optimal alternative is not chosen, the opportunity costs will need to include the optimal profit forgone.^[5] A recent proposal generalised this as adding the incurred expenditure (the “explicit cost”) and the highest net benefit forgone (the “implicit cost”) as opportunity costs,^[128] which is broadly considered equivalent to “economic costs”.^[34,128] Yet, this fails to adequately correct for any competitive disequilibrium of the optimal alternative.

Altogether, four different methodologies have evolved over time and comprise the taxonomy presented here:

- A) Opportunity costs in terms of units of the second-best alternative forgone
- B) Opportunity costs as the net benefit of the second-best alternative forgone
- C) Opportunity costs as the expenditure of the alternative chosen
- D) Opportunity costs as the expenditure of the alternative chosen plus the net benefit of the alternative forgone with the greatest value

Illustrated with two options i and j , where j is the next-best alternative to i , the value of the marginal opportunity costs of option i , OC_i , can be formulated. Marginality^[18] refers here to the change in costs and benefits (or units of option j) when providing/treating one more unit of option i . Also, “next-best” here means “second-best” when referring to methodologies A and B, but it means the alternative with the greatest value when referring to Methodology D. The four methodologies then read:

$$OC_i = u_j \tag{1}$$

$$OC_i = u_j \cdot (B_j - C_j) \tag{2}$$

$$OC_i = C_i \tag{3}$$

$$OC_i = C_i + u_j \cdot (B_j - C_j) \tag{4}$$

where u_j denotes the number of units of the next-best alternative forgone, the net benefit is calculated by subtracting the marginal expenditure of the next-best alternative, C_j , from

its marginal gross benefit, B_j , and C_i is the marginal expenditure of the alternative chosen. Generally, expenditures are a sacrifice, typically of money, and benefits a gain, typically valued as the minimum willingness to trade-off, i.e. pay or sell depending on the perspective, also known as the marginal rate of substitution,^[123,128] or expressed in health outcomes like the quality-adjusted life year, QALY.

As can be seen, Equation (2) extends Equation (1) with the net benefit of the number of units of the second-best option j forgone, and Equation (4) is the sum of Equations (3) and (2).

2.5.2 Existing approaches to estimate the opportunity costs of bed-days

The scoping review of existing applications suitable to estimate the opportunity costs of bed-days identified 2,273 records. After the screening and review procedure, 101 relevant articles remained; see Figure 6 in the Appendix (section 2.9). Applications were generalised and clustered into nine approaches, each of which could be classified under one of the four methodologies of the taxonomy. Sixteen articles applied multiple approaches; for a complete list of included references see Table 5 in the Appendix (section 2.9).

An overview of the nine existing approaches applied for an option (read: patient) i is shown in Table 1, together with the results of a numerical illustration and the new proposals presented later. Note that all approaches require information on an alternative option except for those following Methodology C.

2.5.2.1 Methodology A: Opportunity costs in terms of units of the second-best alternative forgone

Two approaches used the first methodology by expressing units of the second-best alternative as patient-equivalents (approach 1) or treatment-equivalents (approach 2).

Patient-equivalents were calculated in terms of the number of alternative patients that could have been treated using the same resources, e.g. bed-days, differently. Frequently, the alternative patient was (implicitly) approximated by the average patient population likely to occupy that bed. One article additionally adjusted for an occupancy rate of 0.75.^[129]

Treatment-equivalents were calculated in terms of the number of alternative treatments that could have been paid for using the same expenditure incurred differently. Resources like beds are hence assumed to be monetised and the money spent elsewhere within healthcare.

Based on Equation (1), approach 1 and 2 can be written as:

$$OC_i = LOS_i \cdot \frac{1}{LOS_j} (\cdot OCR) \quad (1.1)$$

$$OC_i = C_i \cdot \frac{1}{C_j} \quad (1.2)$$

where LOS_i is the incurred resource consumption of bed-days, LOS_j is the resource consumption of the forgone alternative patient, OCR is the (optional) occupancy rate of bed-days, C_i is the expenditure incurred, and C_j is the expenditure of the forgone alternative use (e.g. treatments). For didactic reasons, fractions have been separated into two terms to demonstrate how to value the units consumed by patient i .

2.5.2.2 Methodology B: Opportunity costs as the net benefit of the second-best alternative forgone

The second methodology was used by four approaches that valued the units measured either monetarily (approach 3) or in terms of the health benefit, usually QALYs, using patient-equivalents (approach 4) and/or local cost-effectiveness thresholds (approach 5 and 6). Not all articles using patient-equivalents reported them separately.

Monetary values took on providers' forgone gross expenditures, payment losses (mostly diagnosis-related groups), or net revenue losses. One article adjusted the revenue in sensitivity analyses by 0–25% to account for an occupancy rate of 0.75–1.00.^[130]

The health benefit was usually expressed as the expected number of QALYs lost as a result of not being able to treat patients using the resources expended. For the patient-equivalents forgone, one study derived QALY-gain values from the published literature.^[131] Another study recently aimed to estimate reimbursement tariffs by multiplying the marginal (gross) benefit with an assumed social value of a QALY of £50,000.^[132] Others quantified the expected health benefit as the QALYs forgone of concurrently disinvested existing interventions,^[133] or, more generally, by dividing the

incurred expenditure by the monetary value assigned to health effects, taking as reference a conversion factor representing the cost-effectiveness of marginal interventions paid for out of the same budget, i.e. the local cost-effectiveness threshold.^[134,135]

Based on Equation (2), approach 3(a-c), 4, 5 and 6 can be written as:

$$OC_i = LOS_i \cdot \frac{C_j}{LOS_j} \quad (2.1a)$$

$$OC_i = LOS_i \cdot \frac{R_j}{LOS_j} \quad (\cdot OCR) \quad (2.1b)$$

$$OC_i = LOS_i \cdot \frac{(R_j - C_j)}{LOS_j} \quad (2.1c)$$

$$OC_i = LOS_i \cdot \frac{B_j}{LOS_j} \quad (2.2)$$

$$OC_i = LOS_i \cdot \frac{B_j \cdot \lambda}{LOS_j} \quad (2.3)$$

$$OC_i = C_i \cdot \frac{1}{\lambda} \quad (2.4)$$

where R_j is the revenue of the forgone alternative patient, B_j the health gain from treatment in terms of QALYs for the forgone alternative patient, and λ is the monetary value assigned to health effects as e.g. expressed in local cost-effectiveness thresholds.

2.5.2.3 Methodology C: Opportunity costs as expenditure of the alternative chosen

The third methodology was used by two approaches, mainly differing in whether to multiply results (approach 7) or present them separately (approach 8).

The (health) economic convention of valuing the actually chosen alternative was widely followed by taking either market prices, national tariffs and payment sources, average expenditures from budgets and accounts, or reference costs. Stated-preference techniques like willingness-to-pay surveys were also used to elicit values.

Given that the opportunity costs of fixed resources like bed-days or clinic slots are not always adequately reflected by the monetary value of prices and payments, especially in the short run, they may be separated from the variable costs related to other consumables.

In the short term, variable costs better indicate cost changes according to changes in resource consumption as no cash savings will be realised for the fixed costs proportion.^[136]

Based on Equation (3), approach 7 and 8 can then be written as:

$$OC_i = LOS_i \cdot \frac{C_i}{LOS_i} \quad (3.1)$$

$$OC_i = LOS_i \cdot \frac{VC_i}{LOS_i} \quad \& \quad LOS_i \quad (3.2)$$

where VC_i is the variable cost proportion of the expenditure incurred.

2.5.2.4 Methodology D: Opportunity costs as the expenditure of the alternative chosen plus the highest net benefit forgone

The fourth methodology was used by one approach (approach 9). Opportunity costs were represented as the (total) economic costs for providers, even though most articles identified “opportunity costs” as only the forgone net revenues; for instance: “The sum of opportunity cost and total cost defines the true cost of a surgical device.”^[137, p.1076]

Based on Equation (4), approach 9 can be written as:

$$OC_i = LOS_i \cdot \left(\frac{C_i}{LOS_i} + \frac{(R_j - C_j)}{LOS_j} \right) \quad (4.1)$$

Table 1. Overview of approaches to value the opportunity costs of bed-days used for patient i

Approach	Description	Equation	Results for patient i
<i>Methodology A: Units of the second-best alternative forgone</i>			
1	Patient-equivalents (of second-best patients j) forgone	$LOS_i * \frac{1}{LOS_j}$ (* OCR)	2
2	Treatment-equivalents forgone for the second-best patients j	$C_i * \frac{1}{C_j}$	1.4
<i>Methodology B: Net benefit of the second-best alternative forgone</i>			
<i>Valuation in terms of money</i>			
3a	Expenditure forgone on the second-best patient-equivalents	$LOS_i * \frac{C_j}{LOS_j}$	£10,000
3b	Revenue forgone from the second-best patient-equivalents	$LOS_i * \frac{R_j}{LOS_j}$ (* OCR)	£12,000
3c	Net revenue forgone from the second-best patient-equivalents	$LOS_i * \frac{(R_j - C_j)}{LOS_j}$	£2,000
5	Gross monetary benefit forgone for the second-best patient-equivalents	$LOS_i * \frac{(B_j * \lambda)}{LOS_j}$	£24,000
New1	Net monetary benefit forgone for the second-best patient-equivalents	$LOS_i * \frac{(B_j * \lambda - C_j)}{LOS_j}$	£14,000
New2	Net monetary benefit forgone for the second-best treatment-equivalents	$C_i * \frac{(B_j * \lambda - C_j)}{C_j}$	£9,800
<i>Valuation in terms of health benefit (typically QALYs)</i>			
4	Gross health benefit forgone for second-best patient-equivalents	$LOS_i * \frac{B_j}{LOS_j}$	1.2
6	Health benefit forgone for expected second-best use	$C_i * \frac{1}{\lambda}$	0.35
New3	Net health benefit forgone for the second-best patient-equivalents	$LOS_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{LOS_j}$	0.7
New4	Net health benefit forgone for the second-best treatment-equivalents	$C_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{C_j}$	0.49
<i>Methodology C: Expenditure of the alternative chosen</i>			
7	Expenditure for the resource consumption incurred	$LOS_i * \frac{C_i}{LOS_i}$	£7,000
8	Separating variable expenditure and non-monetary resource consumption	$LOS_i * \frac{VC_i}{LOS_i}$ & LOS_i	£3,500 & 10
<i>Methodology D: Expenditure of the alternative chosen + highest net benefit forgone</i>			
9	Expenditure incurred + highest net revenue forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(R_j - C_j)}{LOS_j} \right)$	£9,000

New5	Expenditure incurred + highest net monetary benefit forgone	LOS_i	$\left(\frac{C_i}{LOS_i} + \frac{(B_j * \lambda - C_j)}{LOS_j} \right)$	£21,000
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The last column illustrates the marginal opportunity costs of patient i consuming 10 bed-days based on the input data in Table 2. Not all articles used LOS. The equations were rearranged to show how the resource consumption of patient i should be valued; LOS_i was thus included in approach 7 and 8 to make this valuation clearer. The new proposals are labelled with “New”; “New1” (and “New5”, depending on whether the chosen alternative was the sub-optimal choice) are favoured given the minor impact of monetary inflation compared to treatment-equivalents.

B_j : (health) benefit gained per second-best patient, C_i : total expenditure incurred for i , C_j : expenditure incurred per second-best patient, λ : monetary value assigned to QALYs in local cost-effectiveness thresholds, LOS_i : total bed-day consumption of i , LOS_j : length of stay per second-best patient, OCR: occupancy rate, QALY: quality-adjusted life year, R: revenue per patient, VC: variable cost proportion of the expenditure.

2.5.3 Illustrative comparison of approaches for valuing bed-days

To highlight differences between the approaches, an illustrative example with three patients P_1 , P_2 and P_3 is presented. To clarify the concept of making a choice between multiple alternative options, more than two patients are presented here following previous recommendations to avoid framing opportunity costs as binary decision problems.^[122] Also, the second-best use of bed-days is assumed to not lie outside the healthcare sector.

Table 2 contains hypothetical values required for the illustration. Following an agent’s objective of e.g. health or income maximisation, the known case-mix is ranked as specifically as possible (e.g. on a ward level) to identify the patient with the highest net value. The existing approaches express the benefit as either monetary revenue or QALYs, which were chosen to be the highest for patient P_1 here; it is the optimally chosen patient i . Where applicable, this patient is compared to the second-best alternative patient j (more precisely: patient group); in this example patient P_2 and not P_3 . Note that the highest valued patient and the second-best patient are unlikely to be each other’s second-best alternative; this is only true for the special case of identical marginal opportunity costs.

Table 2. Input data to illustrate the approaches to value opportunity costs

Occupancy rate	1.0 ^a		
Cost-effectiveness threshold (£)	20,000/QALY		
Patient(s)	P ₁	P ₂	P ₃
Units (bed-days per patient)	10 ^b	5	5
Expenditure (£ per patient)	7,000 (variable: 3,500)	5,000	5,000
Benefit (£ revenue per patient)	9,000	6,000	5,500
Benefit (QALY gain per patient) ^c	1.3	0.6	0.4

Note that all values are illustrative. Based on the highest (net) benefit expressed either monetarily or in QALYs, patient P₁ is the optimally chosen patient *i*, patient P₂ is the second-best patient *j*, and patient P₃ is the third-best patient.

QALY: quality-adjusted life year.

a: assumes full capacity and that freed beds are efficiently redeployed^[4]

b: excess consumption (not necessarily the total length of stay)

c: attributable to the treatment

The value of the opportunity costs for the 10 bed-days consumed by treating one patient *i* (i.e., what treating that patient is “worth”) according to the nine approaches is shown in Table 1. The results vary widely, even within the same methodology and when standardising the unit of outcome, suggesting that further appraisal of the approaches is needed.

2.5.4 Appraisal of existing approaches

The approach used to value bed-days, and consequently the units in which their costs are expressed, must be chosen to match the decision-making agent’s objective(s). In the illustration based on the existing approaches, different agents like providers, payers, or society may seek to maximise natural units, expenditures, revenues, net revenues, or health outcomes.

Approach 1 and 2 lend themselves for analyses of natural units, e.g. to maximise throughput. Expressing the relative costs of production as the exchange rate between natural units (approach 1) reflects the true value of competing resource consumptions more accurately than the exchange rate between the expenditures associated with the natural units (approach 2) given the independence of monetary inflation. In fact, if the expected exchange value differs from the expected cost value, a change in the optimal choice may occur.^[5] In the example presented in this paper, the expenditure of the 2 patient-equivalents forgone is only valued as 1.4 treatment-equivalents. Hence, an agent

aiming to maximise throughput regards treating patient i less favourable, which likely distorts the bed-days' true value.

Providers aiming to maximise income can readily calculate net benefits in the form of net revenues using Equation (2.1c) of approach 3. The other Equations of approach 3, as well as approach 7 and 8, take merely the expenditure or payment, which makes the strong assumption of prices being at the equilibrium point of the perfectly competitive market model, requiring fulfilment of all conditions characterising such markets.^[18,26] This is unlikely given market imperfections in healthcare of e.g. quasi-monopolies and price controls, information asymmetries, patents and licensing requirements, and non-identical products.^[10,26,31,138] Hence, spending £1 is unlikely to generate a benefit (revenue) equivalent to £1. This is illustrated in Table 2 for patients P_2 and P_3 , for which the bed-day consumption and expenditures were kept identical but the benefits varied, which determined P_2 as second-best patient j and P_3 as third-best patient. Approaches 7 and 8 additionally do not explicitly consider the second-best alternative forgone. Approach 9 aims to correct for alternatives being in competitive disequilibrium, but requires identifying options as optimal and non-optimal. It also does not correct for distortions of the optimal alternative's price, still producing flawed results then.

For payers and societies aiming to maximise health, health outcomes form the relevant benefit. The conversion of expenditures into QALYs (approach 6) has been criticised for the missing link to actually displaced or unfunded services.^[135] More importantly, approach 4, 5 and 6 do not calculate net benefits and may be less suitable for subsequent economic studies; more on this in the discussion. Hence, no approach currently exists that calculates net benefits for bed-days using health outcomes.

2.5.5 Proposing an alternative to valuing bed-days

Expressing the health benefit in monetary terms is exactly what is captured with the net monetary benefit, NMB ,^[139,140] which is defined incrementally as:

$$NMB = \Delta B \cdot \lambda - \Delta C \quad (5)$$

where ΔB is the incremental benefit between two healthcare interventions, λ the monetary value per unit of health benefit gained as e.g. defined by a local cost-effectiveness threshold, and ΔC the incremental expenditure between two healthcare

interventions. Note that the NMB calculates the net benefit as required in Equation (2) of Methodology B. For the purposes here, the idea of valuing health gains monetarily with conventional cost-effectiveness thresholds was exploited as shown in Equation (5). Thus, decision makers aiming to maximise health can account for the net benefit of patient j forgone as follows:

$$OC_i = LOS_i \cdot \frac{(B_j \cdot \lambda - C_j)}{LOS_j} \cdot OCR \quad (2.5)$$

where B_j is the marginal health gain from hospital treatment for the second-best patient and C_j denotes the marginal expenditure incurred on the hospital treatment of the second-best patient, for payers thus the reimbursement payment. Note that the health benefit ought to account for the marginal gain of patients from treatment to avoid the contradictory conclusion that patients in no need of care will benefit the most from a hospital bed (e.g. a perfectly healthy individual with a utility score of 1), and to capture any changes in health occurring without the treatment; cf. discussion. In healthcare settings operating near full capacity and in the presence of an unmet demand from otherwise treated patients awaiting admission, the term OCR is to be omitted.

Applied to the data in Table 2 the opportunity costs of the bed-days consumed by patient i equal £14,000 in terms of net benefits forgone for the second-best patients j . By considering health maximisation as objective and the net monetary value of the forgone QALYs, this differs from the values calculated with the existing approaches of Methodology B, i.e. providers' expenditures of £10,000, revenue of £12,000, net revenue of £2,000, gross monetary benefit of £24,000, and 1.2 gross QALYs forgone. Moreover, if the chosen alternative had not been optimal, Methodology D would need to be used:

$$OC_i = LOS_i \cdot \left(\frac{C_i}{LOS_i} + \frac{(B_j \cdot \lambda - C_j)}{LOS_j} \right) \quad (4.2)$$

However, P_1 was the optimal choice as indicated in Table 3; it had the highest net benefit of all three alternatives, and only for P_1 were the sum of the expenditure and the highest net benefit forgone smaller than the benefit incurred. The true value of the opportunity costs for the 10 bed-days is here thus the forgone second-best net benefit of £14,000.

Table 3. Opportunity cost results of the 10 bed-days used for patient P_1 for decision makers aiming to maximise health.

Patient(s)	P_1 (n=1)	P_2 (n=2 forgone)	P_3 (n=2 forgone)
Expenditure (£ in total)	7,000	10,000	10,000
Benefit (GMB, £ in total)	26,000	24,000	16,000
NMB (benefit-expenditure, £ in total)	19,000	14,000	6,000
Expenditure + highest NMB forgone	21,000	29,000	29,000

GMB: gross monetary benefit, NMB: net monetary benefit, QALY: quality-adjusted life year.

Based on the highest (net) benefit expressed either monetarily or in QALYs, patient P_1 is the optimally chosen patient i , patient P_2 is the second-best patient j , and patient P_3 is the third-best patient. Figures in **bold** correspond to approaches (and values) covered in the overview table.

2.6 DISCUSSION

This paper explored different estimation techniques for valuing the opportunity costs of resources. Although seen as fundamental in defining economics^[5,14,34] and health economics,^[4,125,141] the concept's underlying assumptions are frequently disregarded for reasons of pragmatism. As a result, the special case of perfect competition has become a widespread standard, despite it effectively disconnecting the choice problem from the mutually-exclusive, second-best use forgone. It is hence unsurprising to us that this definition made it into numerous economic textbooks as the convention for estimating opportunity costs,^[34] fuelling the confusion of professional economists and others alike.^[122]

When assigning cost values to resources it is important for researchers to make their assumptions explicit, including on the aim, perspective, the associated consequences, and “any adjustments made to approximate to opportunity costs”.^[142] Incorrectly attaching high cost values may give decision-makers the illusion of potentially large cost savings of a programme that reduces resource consumption, while the actual cost savings may be more modest due to only being realisable on the variable cost components and if the freed fixed resources were almost immediately re-deployed.^[4,143] This is especially true for the short run, during which a high proportion of fixed costs will not change and hence should not influence the value of a particular choice from an economic viewpoint.^[143,144]

As for the imperfectly-marketed resource “bed-days”, the existing approaches to costing produce results that differ widely. When using the framework to appraise the underlying assumptions, it was revealed how approximations of the true value of bed-days may be

flawed and violate economic theory, depending on the chosen perspective. This includes the conventional use of reference costs, as the second-best alternative is usually not explicitly accounted for. Moreover, average costs are unlikely to represent the marginal costs of producing one more unit (i.e., bed-day) as the bulk of treatment costs can be expected to occur towards the beginning of a stay.^[4] More generally, it can be questioned whether it is appropriate to adopt the ideas valid for the competitive market model to the imperfect healthcare market.^[144] Nonetheless, many applications resorted to consider merely expenditures or payments. None of the existing approaches valued the health gain associated with bed-days in terms of the net benefit. Consequently, a novel approach was developed using the net monetary benefit of second-best patients, which are asserted to be the most suitable for decision makers aiming to maximise health within a fixed healthcare budget, such as the National Health Service in the United Kingdom and its counterparts in other healthcare systems.

To value health outcomes monetarily, the idea of using local cost-effectiveness thresholds was followed.^[139,140] Although controversial,^[145] these thresholds are used in actual healthcare decision making.^[146,147] Such thresholds can also be estimated based on displaced services at a system level either theoretically based on the decision maker's preference ^[148,149] or empirically based on the opportunity costs of healthcare spending.^[150] When assuming that expenditures not spent on bed-days could be spent elsewhere in the healthcare system, which is the assumption behind reference costs, a general threshold should be used; otherwise a disease-specific threshold may be more sensible when beds saved have to be filled by alternative patients within the same specialty or setting.

As an alternative to the NMB one could use the net health benefit, NHB;^[151] see Table 1 for the additional Equations. Although illustrative to quantify the expected health benefits forgone, the outcome is then converted to units such as QALYs, which do not have an equivalent expression for other resources and outside the health sector. Hence the NMB as in Equation (2.5) was preferred, whose monetary units also underline its character of being an alternative to conventional methods. Likewise, next to patient-equivalents one could resort to treatment-equivalents, bearing in mind that expenditures encounter monetary inflation and may result in distorted bed-day values (cf. section 2.5.4).

Ideally, the novel approach is used by observing actually displaced treatments or patients in a particular setting. For instance, if Table 2 showed three actual patients, not

patient groups, the 10 bed-days consumed by P_1 could have been used to treat both displaced patients P_2 and P_3 as each consumed 5 bed-days. However, it needs to be acknowledged that such observations are not always practical or indeed possible, e.g. when actual patients do not even present at a healthcare facility given their pre-existing knowledge that they cannot be treated there (e.g. for capacity constraints). To enhance generalisability, a pragmatic compromise may be to use patient groups from the regular patient population awaiting admission to a particular ward. Potential heterogeneity of patients should be taken into account by e.g. considering patient sub-groups. From a payer perspective, specific reimbursement payments may be taken as expenditure for the different patient groups, possibly adjusted for price distortions like subsidies ^[4] or excessively high taxes.^[152] In settings with local cost-effectiveness thresholds, the marginal length of stay, expenditure and health benefit of the forgone patients then need to be determined. These could e.g. be approximated context-specifically with an average from national or local studies. Note that from the healthcare payer perspective the marginal expenditure and length of stay are equivalent to the actual reimbursement payment and length of stay given that without hospitalisation, there is no hospital treatment to pay for nor will patients have consumed any hospital resources. Conversely, the marginal health gain of patients from a particular hospital treatment will depend on the condition analysed in order to account for changes in health without treatment, including e.g. death for otherwise fatal conditions if not medically attended in hospital, and the alleviation and prevention of symptoms or disease for non-life-threatening conditions. Health benefit estimations could be based on the natural history of diseases, representative health data like disability weights from the Global Burden of Disease Study ^[153] or quality-of-life scores for diseased and healthy populations,^[150] and potentially even standard care for conditions for which it would be impracticable or unethical to determine the natural course; see the Appendix for two illustrations of such implementations (section 2.9.1).

Special consideration may be needed for temporary decreases in supply and increases in demand for bed-days following exogenous shocks (i.e., unplanned events) like infectious disease epidemics,^[154] heat waves, cold weather, natural disasters, strikes of healthcare personnel or sudden reductions in funding. For example, for infectious disease outbreaks calculations of total length-of-stay may be subject to time-dependent biases with only a proportion being an “excess” stay,^[143] and the isolation or closure of bays and

wards may lead to additional bed-days lost unoccupied. Altogether, all beds lost attributable to the exogenous shock should be added to the number of bed-days consumed by treating patients during an avoidable event. Adjusting bed occupancy to account for capacity should only be done in situations where there is no excess demand (i.e. no shortages or waiting lists). No opportunity costs will then be attached to the empty beds in terms of health forgone for other patients, and other than the cash value of reducing the idle capacity in the long-term (with associated consequences on marginal expenditures and revenues). However, full capacity does not mean all beds being occupied; besides, there may be other limiting factors than the occupancy rate, e.g. the theatre use rate for surgical patients.

2.6.1 Strengths and Limitations

The taxonomy of methodologies were based on extensive reviews of the concept of opportunity costs, including 22 well-known economic textbooks ^[34] as well as James Buchanan's comprehensive treatise.^[5] Existing applications to value bed-days were searched for in a scoping review due to the aim of this study and the paucity of relevant and consistently used search terms. Included articles covered a wide range of journals, interventions and disease areas, which may point towards the general relevance of and interest in the topic among healthcare professions, as well as the broad applicability for the novel approach.

Although indirect costs using wage rates as proxy for opportunity costs were not explicitly considered, these applications are addressed in approach 3 as the time loss is simply multiplied with a wage rate. Also, in reporting the results of the review the number of articles or applications of each approach was not stated. The intent was to focus on the differences per approach and not on the number of applications per approach, which in any case may be biased towards those that are practical given the data available to authors rather than those based on sound theoretical methodology.

Focusing on "bed-days" has advantages as it is a broadly used resource across indications, a major cost driver and hence influential for all kinds of analyses involving patient stays, relatively easy to measure through "length of stay", and universally used (across countries, time and settings like hospitals, long-term care and mental health facilities). Additionally, the opportunity costs of bed-days lost due to isolation or closure of wards can be calculated on the same scale as those directly consumed by patients. By

identifying bed-days as resources this paper concentrated on the last two steps of costing of identification, measurement, and valuation.^[4,25] As such, the novel approach anchors on the identified resource itself as the most important unit to measure costs. Then continuing to value the resources with the marginal net benefit is important to account for the different health benefits and expenditures associated with alternative options (cf. Methodology B), although a disaggregated presentation may facilitate a broader and more explicit multi-criteria decision analysis framework, e.g. when thinking about the value of reducing waiting lists, or when incorporating non-pecuniary decision factors like emotional distress. Moreover, one could also try to elicit the preferences for bed-days to patients and providers; see e.g. Stewardson et al. (2014)^[155] for a study on the willingness-to-pay of 11 hospital administrators.

Despite the focus on bed-days, the concepts presented in this paper can be readily adapted to other goods and resources used to treat patients, such as operating theatre slots or time spent in a general practitioner clinic, as well as to evaluations with other economic perspectives and optimisation objectives. As the illustration was based on existing applications it considered either health, throughput, or (net) revenue maximisation but not equity concerns.

While the novel approach values opportunity costs with the NMB, it is not used incrementally here to evaluate two or more different healthcare interventions.^[4] A full economic evaluation requires additional input parameters for different interventions, including at least their expenditures and effectiveness. Also note that a broader perspective for the opportunity costs across indications was considered (e.g. the second-best alternative patient for specific wards), while economic evaluations typically compare a new intervention to standard care within indications (which is presumed to be the second-best alternative treatment for specific diseases).

Lastly, adequate costing may be quite complex but attempting to identify the second-best patients improves the existing pragmatic convention as it enhances applied research and decision making by coming closer to the theoretical ideal of how to estimate the true costs of resources. Nonetheless, the confidence one has in the opportunity cost estimates will depend largely on how well the actual second-best use has been defined and measured.

2.7 CONCLUSION

This paper has highlighted an underrated issue in costing whose consequences are often not apparent to decision makers, and which has been shown to confuse professional economists too. To summarise, opportunity costs are inherently linked to choice in economics and the net trade-off cost of the second-best use forgone.

Bearing these theoretical considerations in mind when aiming to estimate the opportunity costs of resources adequately is crucial for sound economic research and decision making. Various methodologies were developed in the past that rely on different assumptions. When using the framework that was developed in this paper to appraise the underlying assumptions, it was found that opportunity costs are often applied to valuing bed-days in ways that are flawed and violate economic theory. For pragmatic reasons, the special case of perfect competition has become a convention for estimating opportunity costs, as is demonstrated through the common use of reference costs and administrative accounting data. By relying solely on the incurred resource consumption, cost factors are effectively disconnected from choice and the second-best alternative use forgone. Researchers should i) be aware of the underlying assumptions and resulting biases when applying these approaches, which frequently remain unmentioned and unquestioned; ii) carefully consider the adequate costing approach dependent on an agent's objective and perspective; and iii) explicitly state any potential implications in a manner that is comprehensible to decision makers. For decision makers aiming to maximise health, a novel alternative for bed-days was proposed that effectively re-connects to the concept of choice and explicitly considers net benefits.

2.8 ACKNOWLEDGEMENTS

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2.9 SUPPLEMENTARY MATERIAL

Table 4. Search syntaxes used for the scoping literature review of existing applications suitable to estimate the opportunity costs of bed-days (last search on 02nd December 2016).

PubMed (NLM)		
#	Searches	Records
1	("bed day" OR "bed days") AND (cost OR costs)	701
2	("bed day" OR "bed days") AND demand*	90
3	("bed day" OR "bed days") AND valu*	139
4	("opportunity cost" OR "opportunity costs") AND ("bed day" OR "bed days")	6
5	("opportunity cost" OR "opportunity costs") AND health*	808
6	("opportunity cost" OR "opportunity costs") AND hospital	254
EconLit (Ovid)		
#	Searches	Records
1	(bed day* and cost*).af.	10
2	(bed day* and demand*).af.	1
3	(bed day* and valu*).af.	2
4	(opportunity cost* and bed day*).af.	0
5	(opportunity cost* and health*).af.	239
6	(opportunity cost* and hospital*).af.	23

NLM: National Library of Medicine

Figure 6. Flowchart of the scoping literature review of existing applications suitable to estimate the opportunity costs of bed-days.

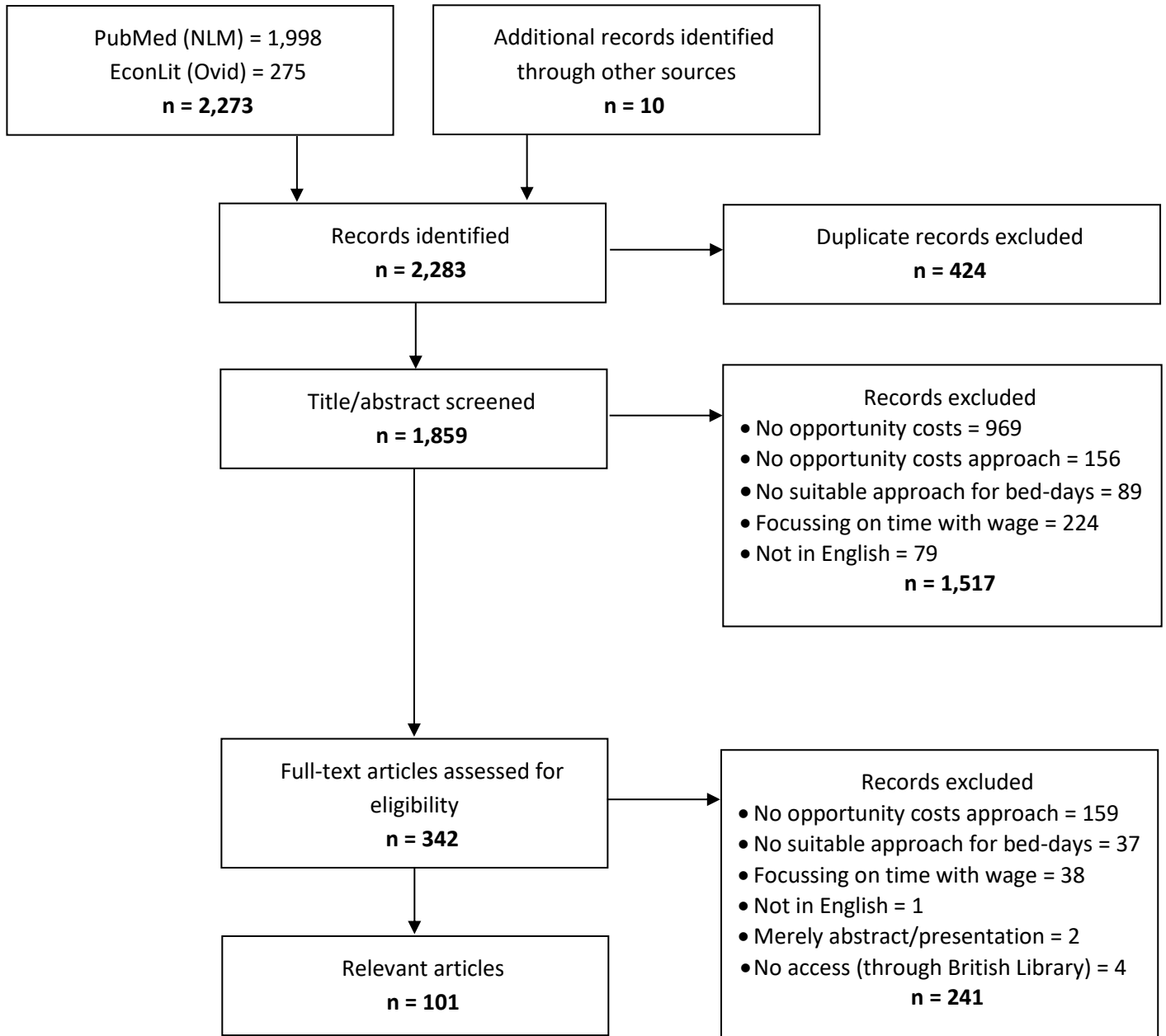


Table 5. Overview of relevant papers detailing existing applications suitable to estimate the opportunity costs of bed-days.

Approach	Description	Records
<i>Methodology A: Units of the second-best alternative forgone</i>		
1	Patient-equivalents (of second-best patients j) forgone	[129,131,156-167]
2	Treatment-equivalents forgone for the second-best patients j	[135,164,167-170]
<i>Methodology B: Net benefit of the second-best alternative forgone</i>		
<i>Valuation in terms of money</i>		
3	Monetary value forgone on the second-best patient-equivalents	[130,156,159,161,162,171-183]
5	Gross monetary benefit forgone for the second-best patient-equivalents	[132]
<i>Valuation in terms of health benefit (typically QALYs)</i>		
4	Gross health benefit forgone for second-best patient-equivalents	[131]
6	Health benefit forgone for expected second-best use	[22,133-135,184]
<i>Methodology C: Expenditure of the alternative chosen</i>		
7	Expenditure for the resource consumption incurred	[130,137,138,143,171,173,175,185-235] [155,236-240]
8	Separating variable expenditure and non-monetary resource consumption	[136,225,241]
<i>Methodology D: Expenditure of the alternative chosen + highest net benefit forgone</i>		
9	Expenditure incurred + highest net revenue forgone	[137,189,191,192,242]

QALY: quality-adjusted life year

2.9.1 Two real-life examples to illustrate the opportunity cost estimation

The following two examples illustrate how implementation of the approaches that were outlined could look like in practice. Some simplifying assumptions were made to ensure clarity.

2.9.1.1 Example 1: Value of bed-days used for patients with acute gastroenteritis in England

Hospital admission of otherwise completely healthy individuals for an episode of acute gastroenteritis is discouraged in England due to the self-limiting nature of symptoms, the limited treatment options, and the risk of admitted patients causing outbreaks of infectious intestinal disease potentially leading to severe service disruptions.^[87] If for instance 40 patients with acute gastroenteritis stayed each 2 days in an acute hospital, the excess resource consumption would have been 80 bed-days. The mean costs for gastroenteritis cases staying in hospital in England in 2015/16 was £1,594 per patient according to the average standard costs list of the National Health Service (NHS).^[243] In order to be able to determine whether treating the gastroenteritis cases in hospital was the optimal alternative, cf. Methodology D, information on their health benefit gained from the treatment was also needed, which was operationalised as the reduction of disutility using the Global Burden of Disease Study: The disability weights for mild, moderate and severe diarrhoea were 0.074, 0.188 and 0.247.^[153] If hospital treatment led to alleviating the gastrointestinal distress symptoms of patients from severe to mild, there would be a gain in health benefit for the patients for the 2 days of experiencing symptoms of $(0.247-0.074)/365*2=0.001$ (the length of stay may also be reduced when shortening the duration of a disease, which were ignored here for simplicity).

Turning to the second-best patients forgone, it was first assumed that their characteristics can be approximated with the average of those for the regularly admitted non-gastroenteritis patient population. Their length-of-stay (LOS) is assumed to be the mean hospital LOS of patients in England in 2015/16 of 5 days,^[244] while the mean costs for all non-gastroenteritis cases was £2,627 per patients.^[243] In addition, a hypothetical hospital revenue (i.e. payments from healthcare payers, i.e. local authorities, to the hospital) of 10% of the expenditure were assumed; i.e. $£2,627*1.1=£2,890$. On average, inpatients will gain much more in terms of health restored and/or maintained when treated

for other conditions than acute gastroenteritis. For instance, the disability weight for the most severe forms of stroke with long-term consequences plus cognition problems is 0.588, while the least severe forms of a mild stroke with long-term consequences is 0.019.^[153] In case timely accessing a free hospital bed for treatment thus prevents or alleviates the most severe forms of a stroke, there would be a potential health benefit gain of $0.588 - 0.019 = 0.569$; cf. the estimated 0.472 QALYs gained per patient over ten years for acute stroke unit care vs. standard care in a general medical ward.^[245] Even higher health gains may be achievable for patients with potentially fatal conditions if they were to die without treatment. For instance, acute myocardial infarction is associated with disability weights of 0.432 on day 1-2 and 0.074 on day 3-28;^[153] if patients thus were to die without treatment but otherwise survived and lived healthy for at least one year, the health gain would be equivalent to $(1 - 0.432)/365 * 2 + (1 - 0.074)/365 * 26 + (1 - 0)/365 * (365 - 2 - 26) = 0.992$. Clinicians may rightfully argue that there will always be a bed made available for emergency patients, or that a constant flow of acute myocardial infarctions will not present themselves even at the largest of emergency departments. Therefore, this illustration will be continued by taking the exemplary health gain of the stroke patients of 0.569.

Furthermore, full capacity was assumed since most NHS hospitals in England operate at full capacity and face waiting lists. As monetary value for the health benefit gained the reference case of the local cost-effectiveness threshold of £20,000/QALY for England and Wales was taken.^[246]

All inputs are shown in Table 6 below, based on Table 2 in the paper:

Table 6. Input data to illustrate the approaches to value the opportunity costs: gastroenteritis cases

Occupancy rate	1.0 ^a	
Cost-effectiveness threshold (£ per QALY)	20,000 ^b	
Patient(s)	P ₁ (acute gastroenteritis cases, n=40)	P ₂ (regularly admitted, non-gastroenteritis patient)
Units (bed-days per patient)	2 (total for 40 patients=80)	5 ^e
Expenditure (£ per patient)	1,594 (variable: 239) ^c	2,627 ^f
Revenue (£ per patient)	-	2,890 ^g
Benefit (QALY gain per patient)	0.001 ^d	0.569 ^h

NHS: National Health Service, NICE: National Institute for Health and Care Excellence, QALY: quality-adjusted life year.

a: assumes full capacity and that freed beds are efficiently redeployed.^[4]

b: local cost-effectiveness threshold value of the reference case in England and Wales.^[246]

c: Mean NHS reference costs of gastroenteritis cases staying in hospital in England in 2015/16, activity-weighted.^[243]

d: Hypothetical mean health benefit gain from hospital treatment for gastroenteritis cases based on disability weights for diarrhoea and an alleviation of a potentially severe to a mild presentation.^[153]

e: Mean hospital length of stay of patients in England in 2015/16.^[244]

f: Mean NHS reference costs of non-gastroenteritis cases staying in hospital in England in 2015/16, activity-weighted.^[243]

g: Mean revenue of hypothetical 10% of the expenditure.

h: Hypothetical mean health benefit gain from hospital treatment for non-gastroenteritis cases based on disability weights for stroke and an alleviation of a potentially severe to a mild presentation.^[153]

Based on this information, the direct expenditure incurred by the gastroenteritis cases was £63,760 (approach 7). When assuming that variable costs make up for 15% of the total costs, preventing the outbreak would have resulted in cash savings of £9,564 (approach 8).

In terms of displaced alternatives, the value of the 80 bed-days is equivalent to having forgone 16 non-gastroenteritis patients (approach 1), 24.3 treatments for the non-gastroenteritis patients (approach 2), a QALY gain between 3.2 to 10.6 (approach 6 and New4), and a monetary value ranging from a forgone hospital profit of £4,203 (approach 3c) to a forgone net monetary benefit for the treatment-equivalents of £212,444 (approach New2); for details see Table 7.

Table 7. Overview of approaches to value the opportunity costs of bed-days used for patients with acute gastroenteritis

Approach	Description	Equation	Results for patient i
<i>Methodology A: Units of the second-best alternative forgone</i>			
1	Patient-equivalents (of non-gastroenteritis patients j) forgone	$LOS_i * \frac{1}{LOS_j} (* OCR)$	16.0
2	Treatment-equivalents forgone for the non-gastroenteritis patients j	$C_i * \frac{1}{C_j}$	24.3
<i>Methodology B: Net benefit of the second-best alternative forgone</i>			
<i>Valuation in terms of money</i>			
3a	Expenditure forgone on the non-gastroenteritis patient-equivalents	$LOS_i * \frac{C_j}{LOS_j}$	£42,032
3b	Revenue forgone from the non-gastroenteritis patient-equivalents	$LOS_i * \frac{R_j}{LOS_j} (* OCR)$	£46,235
3c	Net revenue forgone from the non-gastroenteritis patient-equivalents	$LOS_i * \frac{(R_j - C_j)}{LOS_j}$	£4,203
5	Gross monetary benefit forgone for the non-gastroenteritis patient-equivalents	$LOS_i * \frac{(B_j * \lambda)}{LOS_j}$	£182,080
New1	Net monetary benefit forgone for the non-gastroenteritis patient-equivalents	$LOS_i * \frac{(B_j * \lambda - C_j)}{LOS_j}$	£140,048
New2	Net monetary benefit forgone for the non-gastroenteritis treatment-equivalents	$C_i * \frac{(B_j * \lambda - C_j)}{C_j}$	£212,444
<i>Valuation in terms of QALYs</i>			
4	Gross health benefit forgone for non-gastroenteritis patient-equivalents	$LOS_i * \frac{B_j}{LOS_j}$	9.1
6	Health benefit forgone for expected second-best use	$C_i * \frac{1}{\lambda}$	3.2
New3	Net health benefit forgone for the non-gastroenteritis patient-equivalents	$LOS_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{LOS_j}$	7.0
New4	Net health benefit forgone for the non-gastroenteritis treatment-equivalents	$C_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{C_j}$	10.6
<i>Methodology C: Expenditure of the alternative chosen</i>			
7	Expenditure for the resource consumption incurred	$LOS_i * \frac{C_i}{LOS_i}$	£63,760
8	Separating variable expenditure and non-monetary resource consumption	$LOS_i * \frac{VC_i}{LOS_i} \& LOS_i$	£9,564 & 80
<i>Methodology D: Expenditure of the alternative chosen + highest net benefit forgone</i>			
9	Expenditure incurred + highest net revenue forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(R_j - C_j)}{LOS_j} \right)$	£67,963
New5	Expenditure incurred + highest net monetary benefit forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(B_j * \lambda - C_j)}{LOS_j} \right)$	£203,808

The last column illustrates the marginal opportunity costs of gastroenteritis patients i consuming 80 bed-days.

B: (health) benefit gained per patient, C_i : total expenditure incurred for i , C_j : expenditure incurred per patient, λ : monetary value assigned to QALYs in local cost-effectiveness thresholds, LOS_i : total bed-day consumption of i , LOS_j : length of stay per patient, OCR: occupancy rate, QALY: quality-adjusted life year, R: revenue per patient, VC: variable cost proportion of the expenditure.

When comparing the conventional NHS reference costs to the net monetary benefit forgone for the second-best patients, this illustrative example shows a difference of £63,760 (approach 7) vs. £140,048 (approach New1), which is more than twice the value of the bed-days used for the gastroenteritis cases. This difference is largely driven by the forgone QALY gain and the monetary value assigned to QALYs; e.g. when using the upper-bound cost-effectiveness threshold of NICE of £30,000/QALY, the forgone net monetary benefit resulted in £231,088 or almost four times the figure with the conventional approach 7.

While it may sound plausible that treating gastroenteritis cases is not the optimal choice for bed occupancy, one can investigate this more formally by comparing the net benefits achievable; the highest one determines the optimal choice. For decision makers aiming to maximise health, the net monetary benefit of the forgone non-gastroenteritis patients is already known of £140,048 (cf. approach New1); the net monetary benefit for the gastroenteritis cases (i.e., benefit minus expenditure) still needs to be calculated: $40 \times (0.001 \times £20,000) - £63,760 = £800 - £63,760 = -£62,960$ (an economic loss); see Table 8 below. Thus, the higher net benefit would have been achieved with the non-gastroenteritis cases, which renders the gastroenteritis cases a sub-optimal alternative. Consequently, Methodology D becomes the adequate estimation technique to apply for health-maximising decision makers, with the value of the opportunity costs of the 80 bed-days used for the gastroenteritis cases being actually equivalent to £203,808 (approach New5), providing a strong economic argument for ideally avoiding (or reducing) these hospital stays due to acute gastroenteritis.

Table 8. Opportunity cost results of the 80 bed-days used for gastroenteritis cases using approach New5.

Patient(s)	P ₁ (acute gastroenteritis cases, n=40)	P ₂ (forgone regularly admitted, non-gastroenteritis patients, n=16)
Expenditure (£ in total)	63,760	42,032
Benefit (GMB, £ in total)	800	182,080
NMB (benefit-expenditure, £ in total)	-62,960	140,048
Expenditure + highest NMB forgone	203,808	-20,928

GMB: gross monetary benefit, NMB: net monetary benefit, QALY: quality-adjusted life year. Figures in **bold** correspond to approaches covered in the overview table.

The NMB is higher for P₂ than for P₁, and the “Expenditure + highest NMB forgone” is smaller than the “Benefit (GMB, £ in total)” for P₂ while it is higher for P₁. Everything indicates to that P₁ is the sub-optimal alternative, and the value of the opportunity costs for the 80 bed-days is the “Expenditure + highest NMB forgone” of £203,808.

2.9.1.2 Example 2: Value of bed-days used for competing surgical procedures in Australia

In contrast to example 1 where it was looked at different patients (i.e. cases and displaced alternative patients), example 2 estimates the value of the bed-days used for two competing procedures in the same patients, thus forgoing the use of bed-days for treating patients with one procedure in favour of using a second procedure.

This example is based on a study comparing total laparoscopic hysterectomy (TLH) to total abdominal hysterectomy (TAH) for the treatment of early stage endometrial cancer in two modelled cohorts of 1,000 patients each in Australia.^[247] For simplicity it is assumed that i) these two constitute the only alternatives and ii) resources for operations were at full capacity. Thus, the value of the bed-days used for the laparoscopic procedures are estimated in terms of the forgone abdominal procedures. The study used a higher monetary value of AU\$64,000/QALY for Australia, and the results published for 6-month post-surgery were used; see Table 9. No information on the revenue was provided, which is why the corresponding approaches 3b, 3c, and 9 were omitted.

Table 9. Input data to illustrate the value of the opportunity costs: total laparoscopic hysterectomy in terms of total abdominal hysterectomy.

Occupancy rate	1.0 ^a	
Cost-effectiveness threshold (AU\$ per QALY)	64,000 ^b	
Patient(s)	P ₁ (TLH, n=1,000)	P ₂ (TAH)
Units (bed-days per patient)	3.76 (total for 1,000 patients=3,760)	7.31
Expenditure (AU\$ per patient)	12,124	15,870
Revenue (AU\$ per patient)	-	- ^c
Benefit (QALY gain per patient)	0.86	0.82

AU\$: Australian dollar, EQ-5D: EuroQol five dimensions, LOS: length of stay, QALY: quality-adjusted life year, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy.

All values were reflecting the situation as of 6-month post-surgery (i.e., including the LOS of readmissions, expenditure on all health services used, and the EQ-5D scores at month 6).

a: assumes full capacity and that freed beds are efficiently redeployed.^[4]

b: Estimated for Australia.

c: Not provided.

For the 1,000 laparoscopic procedures, 3,760 bed-days were used in total at direct expenditures of AU\$12.1 million (approach 7). The forgone abdominal procedures would have resulted in net monetary benefits of AU\$18.8 million (approach New1); about 1.55 times the value of the direct expenditure incurred.

Table 10. Overview of approaches to value the opportunity costs of bed-days for total laparoscopic hysterectomy surgery

Approach	Description	Equation	Results for patient i
<i>Methodology A: Units of the second-best alternative forgone</i>			
1	Patient-equivalents (of TAH patients j) forgone	$LOS_i * \frac{1}{LOS_j} (* OCR)$	514.4
2	Treatment-equivalents forgone for TAH patients j	$C_i * \frac{1}{C_j}$	764.0
<i>Methodology B: Net benefit of the second-best alternative forgone</i>			
<i>Valuation in terms of money</i>			
3a	Expenditure forgone on TAH patient-equivalents	$LOS_i * \frac{C_j}{LOS_j}$	AU\$8,162,955
3b	Revenue forgone from the TAH patient-equivalents	$LOS_i * \frac{R_j}{LOS_j} (* OCR)$	n/a
3c	Net revenue forgone from the TAH patient-equivalents	$LOS_i * \frac{(R_j - C_j)}{LOS_j}$	n/a
5	Gross monetary benefit forgone for the TAH patient-equivalents	$LOS_i * \frac{(B_j * \lambda)}{LOS_j}$	AU\$26,993,817
New1	Net monetary benefit forgone for the TAH patient-equivalents	$LOS_i * \frac{(B_j * \lambda - C_j)}{LOS_j}$	AU\$18,830,862
New2	Net monetary benefit forgone for the TAH treatment-equivalents	$C_i * \frac{(B_j * \lambda - C_j)}{C_j}$	AU\$27,968,471
<i>Valuation in terms of QALYs</i>			
4	Gross health benefit forgone for TAH patient-equivalents	$LOS_i * \frac{B_j}{LOS_j}$	421.8
6	Health benefit forgone for expected second-best use	$C_i * \frac{1}{\lambda}$	189.4
New3	Net health benefit forgone for the TAH patient-equivalents	$LOS_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{LOS_j}$	294.2
New4	Net health benefit forgone for the TAH treatment-equivalents	$C_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{C_j}$	437.0
<i>Methodology C: Expenditure of the alternative chosen</i>			
7	Expenditure for the resource consumption incurred	$LOS_i * \frac{C_i}{LOS_i}$	AU\$12,124,000
8	Separating variable expenditure and non-monetary resource consumption	$LOS_i * \frac{VC_i}{LOS_i} \& LOS_i$	AU\$1,818,600 & 80
<i>Methodology D: Expenditure of the alternative chosen + highest net benefit forgone</i>			
9	Expenditure incurred + highest net revenue forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(R_j - C_j)}{LOS_j} \right)$	n/a

New5	Expenditure incurred + highest net monetary benefit forgone	LOS_i $* \left(\frac{C_i}{LOS_i} + \frac{(B_j * \lambda - C_j)}{LOS_j} \right)$	AU\$30,954,862
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The last column illustrates the marginal opportunity costs of patients *i* consuming 3,760 bed-days.

AU\$: Australian dollar, B: (health) benefit gained per patient, C_i: total expenditure incurred for *i*, C_j: expenditure incurred per patient, λ: monetary value assigned to QALYs in local cost-effectiveness thresholds, LOS_i: total bed-day consumption of *i*, LOS_j: length of stay per patient, n/a: not available, OCR: occupancy rate, QALY: quality-adjusted life year, R: revenue per patient, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, VC: variable cost proportion of the expenditure.

Moreover, if looking at the different net benefits achievable again (see Table 11), the net monetary benefit for the forgone TAH procedures is lower than for TLH, and for the TLH procedures the “Expenditure + highest NMB forgone” is lower than the “Benefit (GMB, AU\$ in total)” (while higher for the TAH procedure). The TAH procedures are thus a sub-optimal alternative compared to TLH, leaving TLH as the optimal choice here and the value of the opportunity costs for the 3,760 bed-days being equivalent to the second-best net monetary benefit forgone of AU\$18.8 million (approach New1).

Table 11. Opportunity cost results of the 3,760 bed-days used for total laparoscopic hysterectomy procedures using approach New1.

Occupancy rate	1.0 ^a	
Cost-effectiveness threshold (AU\$ per QALY)	64,000 ^b	
Patient(s)	P ₁ (TLH, n=1,000)	P ₂ (forgone TAH procedures, n=514.4)
Expenditure (AU\$ in total)	12,124,000	8,162,955
Benefit (GMB, AU\$ in total)	55,040,000	26,993,817
NMB (benefit-expenditure, AU\$ in total)	42,916,000	18,830,862
Expenditure + highest NMB forgone	30,954,862	51,078,955

AU\$: Australian dollar, GMB: gross monetary benefit, NMB: net monetary benefit, QALY: quality-adjusted life year, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy. Figures in **bold** correspond to approaches covered in the overview table.

The situation is reversed here; the NMB is higher for P₁ than for P₂, and the “Expenditure + highest NMB forgone” is smaller than the “Benefit (GMB, AU\$ in total)” for P₁ while it is higher for P₂. P₂ is thus the sub-optimal alternative, and the value of the opportunity costs for the 3,760 bed-days is the forgone “Net monetary benefit (AU\$ in total)” of AU\$18,830,862.

3 COSTING THE WINTER BED PRESSURE DUE TO ACUTE GASTROENTERITIS

Previously, chapter 2 developed the general idea of how to cost the resource “bed-days” in healthcare settings, particularly from the perspective of a decision maker aiming to maximise population health. Next, chapters 3 to 5 turn towards the practical application of these ideas.

For illustration, norovirus-associated gastroenteritis (in short: norovirus, NoV) is used as a case study given that it causes disruptive outbreaks in hospitals, and its recurring bed pressures during winter are a major public health concern (cf. section 1.3.3). In chapter 3, the conventional costing technique is used by averaging accounting expenditures, that is, using NHS “reference costs”. This analysis utilises a routine dataset, but for the first time adjusts for its missing values. Given that the dataset records all bed-days lost due to “norovirus-like symptoms”, as the observations are called by NHS England, an attempt is made of inferring outbreaks from the data using conventional outbreak definitions for norovirus (of ≥ 2 cases limited in time and place).

Title of paper, name of authors and affiliations:

Burden, duration, and costs of hospital bed closures due to acute gastroenteritis in England per winter, 2010/11–2015/16.

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Publication status: published in *Journal of Hospital Infection*, 2017. Additional unpublished material is presented in sections 3.9.3 to 3.9.6.

3.1 COVER SHEET OF RESEARCH PAPER 2

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Principal Supervisor	Prof. Mark Jit
Thesis Title	The true cost of epidemic and outbreak diseases in hospitals

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Journal of Hospital Infection		
When was the work published?	25.05.2017		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the study, developed the imputation methods, retrieved the data, performed the analysis, interpreted results, and drafted the paper and subsequent revisions during the peer-review. MJ, JVR, and SRD equally provided critical comments on the methodology, analysis, interpretation of results, and the different versions of the paper. I presented a poster of this study at the
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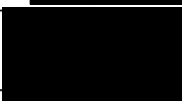
	Lancet's Public Health Science conference (Cardiff, 2016), and gave presentations at the 6th International Calicivirus Conference (Savannah, USA, 2016) and the Vaccine Centre Student Event (LSHTM, 2016).
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Student Signature:



Date: 27.01.2018

Supervisor Signature:



Date: 27.01.2018

3.2 SUMMARY

Background: Bed closures due to acute gastroenteritis put hospitals under pressure each winter. In England, the National Health Service (NHS) has monitored the winter situation for all acute Trusts since 2010/11.

Aim: To estimate the burden, duration, and costs of hospital bed closures due to acute gastroenteritis in winter.

Methods: A retrospective analysis of routinely collected time-series data by NHS England of beds closed due to diarrhoea and vomiting was conducted for the winters 2010/11 to 2015/16. Two key issues were addressed by imputing non-randomly missing values at provider-level, and filtering observations to a range of dates recorded in all six winters. The lowest and highest value imputed were taken as best and worst case scenarios. Bed-days were costed using NHS reference costs, and considering potential staff absence costs based on previous studies.

Findings: In the best-to-worst case, a median 88,000–113,000 beds were closed due to gastroenteritis each winter. Of these, 19.6–20.4% were unoccupied, respectively. On average, 80% of providers were affected, and had closed beds for a median of 15–21 days each winter. Hospital costs of beds lost unoccupied were £5.7–£7.5 million, which increased to £6.9–£10.0 million when including staff absence costs due to illness.

Conclusions: The median number of hospital beds closed due to acute gastroenteritis per winter was equivalent to all general and acute hospital beds in England being unavailable for a median of 0.88 to 1.12 days. Costs for hospitals are high but vary with closures each winter.

3.3 INTRODUCTION

In healthcare settings, acute gastroenteritis (i.e., diarrhoea and vomiting) is a common source of disruption for routine care due to the sudden onset of symptoms, and the potential for enteric pathogens to cause outbreaks of infectious nature.^[231] In 2004, hospital outbreaks of acute gastroenteritis have been estimated to cost the National Health Service (NHS) in England £115 million annually.^[204] The main elements making up this cost were a decrease in the supply of available beds (when “closed” due to acute gastroenteritis, i.e. these beds have become unavailable for admissions) and staff absence due to illness. Between 2009–2011, Public Health England recorded a mean of 15,000 bed-days lost and 3,400 cases among staff per year from voluntarily reported hospital outbreaks (primarily of norovirus).^[174] This underestimates the national burden given regional variation in reporting leading to an estimated under-ascertainment of approximately 20%.^[163]

Due to increased demand each winter, the impact of reduced numbers of available beds supplied in hospitals is greater than in the rest of the year. In England, the NHS has been monitoring the performance of all acute hospital Trusts each winter since 2010/11, which includes mandatory reporting of any bed closed due to diarrhoea and vomiting on weekdays.^[248] These compulsory reports thus allow for a comprehensive overview of the impact of all causes of acute (infectious and non-infectious) gastroenteritis on bed-days lost nationwide during six winters across seven years.

This study aimed to provide updated estimates for the burden, duration and costs of all forms of acute gastroenteritis impacting hospital bed availability in England during winter. In addition to investigating the closure duration, it was also explored whether the outbreak duration of infectious gastroenteritis could be traced in the data by following conventional definitions for outbreaks of norovirus,^[184,224,225] which has become the key enteric pathogen across all ages worldwide, particularly in countries that introduced rotavirus vaccination (like the USA).^[164,220] Estimates were also compared across winters in order to provide insights into variation across the whole hospital system.

3.4 METHODS

3.4.1 Data

Using NHS England's winter situation reports for 2010/11 to 2015/16, all available records were obtained of occupied and unoccupied beds closed due to diarrhoea and vomiting, and the total number of general and acute beds available (including escalation beds but excluding maternity and mental health beds).^[248] Records were only available at the level of Trusts, which may contain multiple hospitals and/or wards within a hospital. Bed figures were reported on weekdays only (reflecting the number for the previous day), and figures for weekends and bank holidays reflect the last day of that respective period.^[248] Suspected errors in reporting or mis-coding encountered in the data were treated as missing values (n=0.54%; see Discussion).

3.4.2 Statistical analysis

Two key issues in the data were addressed for a reliable comparison across winters. First, one-third of values were missing due to weekends and bank holidays. To account for this, values were imputed at provider-level through last-observation carried forward, LOCF, and next-observation carried backward, NOCB. Thereby, records for Thursdays were carried forward to inform the missing values for Fridays and Saturdays (with LOCF), and records for Sundays were carried backwards to impute values for Saturdays and Fridays (i.e., NOCB). To avoid biasing results systematically upwards when closed beds were recorded only before but not after the missing values (and vice versa), the lowest value imputed with either LOCF or NOCB was considered as conservative best case scenario. The highest value imputed with either imputation strategy was also considered, as worst case scenario.

Second, recording lengths and periods are determined flexibly by NHS officials each winter and varied from 13 to 21 weeks between November to March. The analysis was restricted to an overlapping range of dates recorded in all six winters (30th November to 20th February; i.e., 83 days or nearly 12 weeks) after imputing missing values.

Descriptive statistics are provided with the median and interquartile range (IQR) to highlight variation between winters. In order to investigate the relationship between unoccupied and occupied beds closed per day Pearson's correlation coefficient was

calculated. To visualise any trend across winters, locally weighted regression curves were fitted to the time-series of all beds closed (with lowest imputations) across all winters, and linear regression curves interrupted between the winters of 2012/13 and 2013/14. Data (with lowest imputations) were also scaled to the highest daily number per winter using the unadjusted periods (of between 13 to 21 weeks) to identify within-winter variations.

3.4.3 Quantifying the duration of bed closures

To analyse the duration of bed closures the length of consecutive days closed were counted per provider in the imputed datasets.

In order to explore whether outbreaks of infectious gastroenteritis could be traced in the data, conventional definitions were followed for outbreaks of norovirus as the key enteric pathogen: >1 case for >1 day; symptom onset within ± 48 hours.^[184,224,225] First, records were removed of isolated occurrences of one bed closed for one day and no other closure within ± 48 hours. Then, bed closures reported within ± 48 hours were connected and analysed as part of one sustained outbreak. In scenario analyses, sequences were removed with beds being closed on the first or last day of recording, as well as on the second (to last) day to account for the ± 48 hours period. Given that the removal of censored durations biases results when excluding the longest-lasting closures, it was also explored including the duration of outbreaks truncated to the overlapping range of dates from the raw data again, where possible, and only removed the remaining censored outbreaks (i.e. for those two winters that defined the start and end date of the filtered range of dates; see Appendix in section 3.9).

3.4.4 Cost analysis

The financial costs of acute gastroenteritis were estimated from the perspective of hospitals based on the number of unoccupied beds closed and staff absence costs.

Financial costs for hospitals arise from revenue losses of beds closed unoccupied as no (additional) patients can be treated in the unused beds. Beds closed occupied do not represent a financial loss for hospitals in the same sense; this is discussed further in the Discussion.

Staff absence costs were also considered given their importance, although they are not recorded in NHS England’s winter situation reports. The proportion of staff absence costs on the total costs from previous studies of outbreaks of acute gastroenteritis in England and Scotland were 0.245 and 0.174, respectively.^[204,249]

The total financial and economic costs per winter was estimated as:

$$TC_i = (BD_i \cdot C \cdot 1 / (1 - S_i)) \quad (\text{Eq. 1})$$

, where TC represents the total costs, BD the median total of all occupied and unoccupied beds closed, C the average NHS reference costs for elective and non-elective inpatient excess bed-days in 2014/15,^[232] S the proportion of staff absence costs, and i takes on the lowest and highest value (read: imputation and proportion) for the best-to-worst case scenarios.

All analyses were performed in R version 3.2.2 using RStudio.^[126]

3.5 RESULTS

3.5.1 Winter burden of hospital beds closed due to acute gastroenteritis

On average 80% of general and acute NHS hospital Trusts have closed beds due to diarrhoea and vomiting each winter. The median number of beds closed per winter was 88,000 (IQR: 71,000–123,000) to 113,000 (IQR: 88,000–151,000) with the lowest-to-highest imputation. Of these, 19.6–20.4% were unoccupied, respectively, with a median 17,000 (IQR: 13,000–23,000) to 23,000 (IQR: 17,000–31,000) beds per winter. Occupied and unoccupied beds closed per day were strongly positively correlated (best case $r = 0.91$, worst case $r = 0.89$).

During winter, the daily total general and acute hospital capacity in England was reported as a median 100,000 (IQR: 99,500–101,000) to 101,000 (IQR: 99,900–102,000) bed-days with the lowest-to-highest imputation. Of these, 1.1–1.3% were closed due to diarrhoea and vomiting.

The highest numbers of occupied and unoccupied beds closed was found for the winters in 2011/12 and 2012/13, irrespective of the imputation scenario (see Table 12). The number of beds closed has declined from a peak of 135,000–168,000 in 2012/2013 to

37,800–50,100 in 2015/2016, with a corresponding trend for unoccupied beds. Since 2013/14, the level of the slope of the linear fit decreased and its direction became negative even for the data with the highest imputations (see Figure 7), representing a decline in bed closures due to diarrhoea and vomiting in recent winters. Furthermore, when scaling the data to the day with the highest number of beds closed each winter (for the unadjusted periods), a peak occurred either in December or February in most winters even when using the lowest imputations, occasionally with peaks in both months, next to an upwards linear trend for most winters (see Figure 9 in the Appendix, section 3.9.2).

Table 12. Hospital beds unavailable due do diarrhoea and vomiting in England, 2010/11 to 2015/16 (November 30 to February 20)

Winter season	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
No. of Trusts closing beds, per winter						
Trusts affected (% of total)	129 (78.2)	138 (84.1)	134 (84.3)	127 (80.9)	128 (83.7)	101 (66.4)
No. of beds closed, per winter						
Best case	98,500	135,000	131,000	68,600	78,100	37,800
Worst case	123,000	168,000	161,000	83,800	102,000	50,100
No. of unoccupied beds closed, per winter						
Best case	20,800	25,100	24,100	13,300	13,800	7,100
Worst case	27,600	34,000	31,700	17,200	18,400	9,600
No. of sustained bed closures in total, per winter						
Best case	476	512	558	503	521	388
Worst case	477	512	571	512	532	396
Duration of sustained bed closures in days, per winter						
Best case: mean (SD)	7.2 (10.0)	8.8 (12.0)	8.2 (11.9)	6.1 (8.6)	6.2 (8.4)	5.0 (7.7)
Worst case: mean (SD)	8.5 (10.1)	10.1 (12.0)	9.3 (11.8)	7.1 (8.7)	7.3 (8.3)	6.1 (7.7)
Best case: median (IQR)	3 (1–8)	4 (2–10)	4 (1–10)	3 (1–8)	3 (1–7)	2 (1–6)
Worst case: median (IQR)	5 (3–10)	6 (3–12)	5 (3–11)	4 (3–8)	5 (3–8)	4 (2–7)
No. of potential outbreaks of infectious gastroenteritis, per winter						
Best case	393	463	492	430	443	321
Worst case	348	408	437	383	419	304
Duration of potential outbreaks of infectious gastroenteritis in days, per winter						
Best case: mean (SD)	8.8 (11.5)	9.7 (12.6)	9.4 (12.7)	7.2 (9.4)	7.4 (9.2)	6.2 (9.8)
Worst case: mean (SD)	12.0 (13.9)	12.9 (14.5)	12.4 (14.0)	9.9 (11.3)	9.5 (10.7)	8.2 (10.7)
Best case: median (IQR)	4 (2–11)	5 (2–12)	4 (2–11)	4 (2–10)	4 (2–9)	3 (1–7)
Worst case: median (IQR)	7 (4–14)	8 (4–15)	6 (3–16)	6 (3–13)	6 (3–12)	5 (3–10)
Financial costs of unoccupied beds closed in million £, per winter						
Best case (excl. staff absence)	8.2 (6.8)	10.0 (8.2)	9.5 (7.9)	5.3 (4.4)	5.5 (4.5)	2.8 (2.3)
Worst case (excl. staff absence)	12.0 (9.0)	14.7 (11.1)	13.8 (10.4)	7.5 (5.6)	8.0 (6.0)	4.2 (3.2)
Economic value of occupied and unoccupied beds closed in million £, per winter						
Best case (excl. staff absence)	39.0 (32.2)	53.4 (44.1)	51.7 (42.7)	27.2 (22.5)	31.0 (25.6)	15.0 (12.4)
Worst case (excl. staff absence)	53.5 (40.4)	73.1 (55.2)	69.7 (52.6)	36.3 (27.4)	44.2 (33.4)	21.7 (16.4)

The total number of Trusts has been decreasing over time from 165 in 2010/11 to 152 in 2015/16 due to mergers and restructuring in the NHS. Results do not include the scenario analyses of removing censored durations (see Appendix, section 3.9.1). For the “No. of potential outbreaks of infectious gastroenteritis”, the best case is higher than the worst case given that fewer sustained closures were connected. Costs represent 2014/2015 values of pound sterling.

IQR: interquartile range, NHS: National Health Service, SD: standard deviation.

3.5.2 Duration of bed closures due to acute gastroenteritis

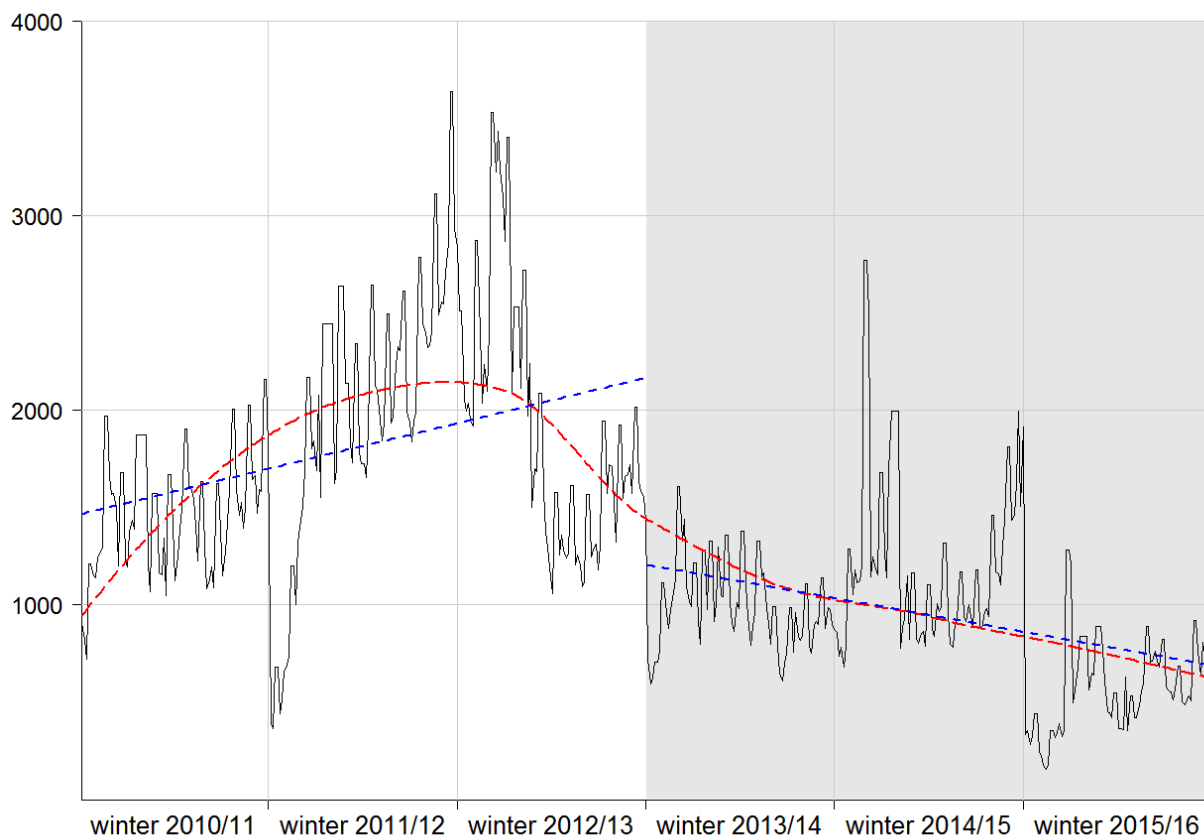
The duration of 2,960–3,000 sustained closures were analysed across the six winters in the lowest-to-highest imputation. A median of three sustained closures per provider was found each winter with both imputations (full range 0–14). The median total of days with beds closed per provider was 15 and 21 (range 0–83). Each closure lasted between a median 3 (IQR: 1–8) to 5 (IQR: 3–10) days and a mean 7.0 (SD 10.1) to 8.2 days (SD 10.1).

Following the methodology to trace the potential outbreak duration of infectious gastroenteritis resulted in 2,540–2,300 sustained closures in the lowest-to-highest imputation. Durations were found of a median 4 (IQR: 2–10) to 6 (IQR: 3–13) days and a mean 8.3 (SD 11.1) to 10.9 days (SD 12.8). The scenario analyses of excluding censored durations did not change the median while the mean decreased to 8.0–10.6 or 6.7–9.1 days, depending on whether or not the duration of truncated outbreaks from the raw data were included (see Appendix in section 3.9).

3.5.3 Costs of unoccupied beds closed due to acute gastroenteritis for hospitals

The financial cost for hospitals corresponding to the median of unoccupied beds closed was £5.7–£7.5 million in England per winter (with the range representing the lowest-to-highest imputations). This increased to £6.9–£10.0 million when including staff absence due to illness; see Table 12.

Figure 7. Time trend of the daily number of hospital beds closed due to diarrhoea and vomiting in England across winters, 2010/11 to 2015/16 (November 30 to February 20).



Black line represents the data (with highest imputations), red long-dashed line the locally weighted regression fit, and blue dashed line the linear regression fit (interrupted between winters 2012/13 and 2013/14).

3.6 DISCUSSION

This study provides up-to-date estimates for the burden, duration and costs of all forms of acute gastroenteritis impacting hospital bed availability in England for six winters across seven years. Although only about 1.1–1.3% of all general and acute beds were closed due to diarrhoea and vomiting in the last six winters per day, the total of the median number of beds closed per winter equalled about the entire median total capacity in England per day ($88,000/100,000$ to $113,000/101,000 = 0.88$ to 1.12 days). The data were subject to variation between winters: The burden of bed closures was highest in the first

three winters recorded, which coincided with rotavirus vaccine introduction in July 2013,^[180,227,233] and with the emergence of a novel norovirus strain mutation (2012/Sydney).^[132,179] Fluctuation of numbers were seen also with the scaled data showing a second peak in mid-February in most winters (see Figure 9 in the Appendix, section 3.9.2).

Although occupied beds closed do not represent a financial revenue loss for hospitals, these beds are blocked for alternative patients and opportunity costs may arise from the lost opportunity to treat the patient who would have been admitted if the bed was available. Thus, if one was to assume that the entire period that a bed was closed due to diarrhoea and vomiting would have been avoidable, the economic value for hospitals of all beds closed occupied and unoccupied was £29–£37 million per winter (and £35–£49 million when including staff absence costs). However, this estimation thus assumes that patients who occupied closed beds would have been discharged were the bed not closed, i.e. the length of stay of the patient would always be reduced, and that there are no other clinical or operational reasons that a discharge might be delayed; considering such time-dependent biases and competing risks in the underlying discharge process was beyond the scope of this study.^[221]

3.6.1 Comparison with previous work

The strong positive correlation between unoccupied beds closed and occupied beds closed is likely due to closures of bays with >1 bed, which supports previous research on the impact of physical proximity of cases and the structural design of wards.^[176,224]

Compared to the estimated potential outbreak duration of infectious gastroenteritis of a median 4–6 days and a mean 8.3–10.9 days in this paper, previous studies in England observed an average outbreak duration of 9.2 (95%–CI: 6.5–11.9) days per ward closure to new admissions in England in 2002/03,^[175,204] and a median length of 6–7 days from Public Health England’s surveillance system of voluntarily-reported norovirus outbreaks in hospitals between 2009/10–2014/15.^[174] Most differences may be explained by NHS England recording only the winter periods instead of annually, and records being made per Trust and not per outbreak despite that several distinct outbreaks may be occurring at the same time. Nonetheless, the short incubation and fast spread of many infectious forms of gastroenteritis may suggest local confinement.^[228]

Previously, the costs of infectious gastroenteritis outbreaks in England were estimated in 2004 at £115 million per year based on a top-down approach using data from 1994/95 and 2002/03.^[204,219] Differences to the estimates in this paper may be explained by a calculation per annum instead of per winter, a top-down vs. bottom-up approach to costing, the baseline year being a high-incidence year for norovirus with novel strain emergence and unusually high summer activity that had a seemingly worse impact than the strain emergence in 2012.^[174,222] Also, the number of laboratory reports for norovirus have declined in total numbers in recent years,^[165] possibly because of milder winters, a decline in the natural year-to-year variability of the burden overall since the late 1990s/early 2000s, or other unrelated factors like reporting practices. Also, although the actual opportunity costs may not be equivalent to the excess bed-day value, if one was to uprate the weighted average of the unit costs per bed-day for various medical specialties considered in Lopman et al.^[204] to represent 2014/15 values,¹⁴ the estimates of the study presented here would increase by 12%; as such the values can still be considered conservative.

3.6.2 Strengths and Limitations

To the best of the authors' knowledge, this study is the first to address both the missing values and different recording lengths in NHS England's hospital data. Previous studies relied on raw data to estimate the number of beds closed due to diarrhoea and vomiting for four winters (2010/11–2013/14),^[177] and to provide a comprehensive overview of hospital performance indicators for an overlapping range of weeks (week 45–6) for five winters (2010/11–2014/15).^[178]

The data analysed in this study are considered to be the best available information by NHS to monitor the NHS hospital performance during winters.^[248] Nonetheless, the speed of collection allows only minimal validation of the raw data.^[248] This may explain why a small fraction of cells in the spreadsheets were coded with a “-“ (n=163; 0.20% of all cells), and a “0” for the general bed availability (n=273; 0.34%). All of them were considered as missing values, and thus accounted for in the subsequent imputations. Despite these efforts, the estimated daily capacity of a median 100,000–101,000 general and acute hospital beds per day is 4% lower than the official number of a median 105,000 for general and acute beds available daily in the quarters 4 and 1 for the winters 2010/11–2015/16,^[230] which may give an indication of the potential under-ascertainment.

Given that the data represent only a once-daily snapshot, it is possible for the status of beds to have changed within the same day (e.g. an occupied bed closed may have become an unoccupied bed closed when patients were discharged). Interestingly, when assuming that beds were not closed independently, the median number of beds closed occupied was higher for Sundays than for Thursdays (Wilcoxon signed-rank test: $P=0.002$), while the change in beds closed unoccupied was statistically insignificant ($P=0.4$). This increase in patients occupying beds due to diarrhoea and vomiting towards the end of weekends while the numbers of unoccupied beds remain constant may thus be a further indication for an underlying infectious cause.

Furthermore, when comparing central tendencies (mean, median) and measures of spread (SD, IQR) for the daily number of beds closed between the raw data and the imputations, the lowest imputation underestimated both central tendencies and measures of spread of the raw data while the highest imputation overestimated it (data not shown). With the information available, it is not possible to determine where exactly the number of beds closed lies on the range of the lowest to highest imputations; this inaccuracy is unavoidable though due to the values missing.

Despite the declining trend in the number of beds closed per winter, the time-series may not be long enough to capture all relevant events given that e.g. cyclical norovirus strain emergence occurs only about every 3–4 years,^{15,16} with only the latest mutation in 2012 captured in the dataset. There is also a known background circulation of norovirus in the summer.^[165]

In addition, cases of acute gastroenteritis seen in hospitals may potentially be community-acquired or of nosocomial origin.^[250] Apart from in hospitals, substantial costs from infectious intestinal disease also arise in the community that have not been considered here.^[167,229]

3.7 CONCLUSIONS

Bed closures due to acute (infectious and non-infectious) gastroenteritis put general and acute NHS hospitals under pressure each winter, with all hospital beds in England being unavailable for an equivalent of 0.88 to 1.12 days. About 19.6–20.4% of closed beds were lost unoccupied. If the data were collected daily over an identical time period, the imputation strategies of the analysis would have been superfluous and thus the data would

allow a more precise surveillance within and across years. Future research needs to quantify the opportunity costs for patients in the NHS, and account for time-dependent biases.

3.8 ACKNOWLEDGEMENTS

We would like to thank all general and acute hospital Trusts in England for the collection and submission of data to the National Health Service (NHS).

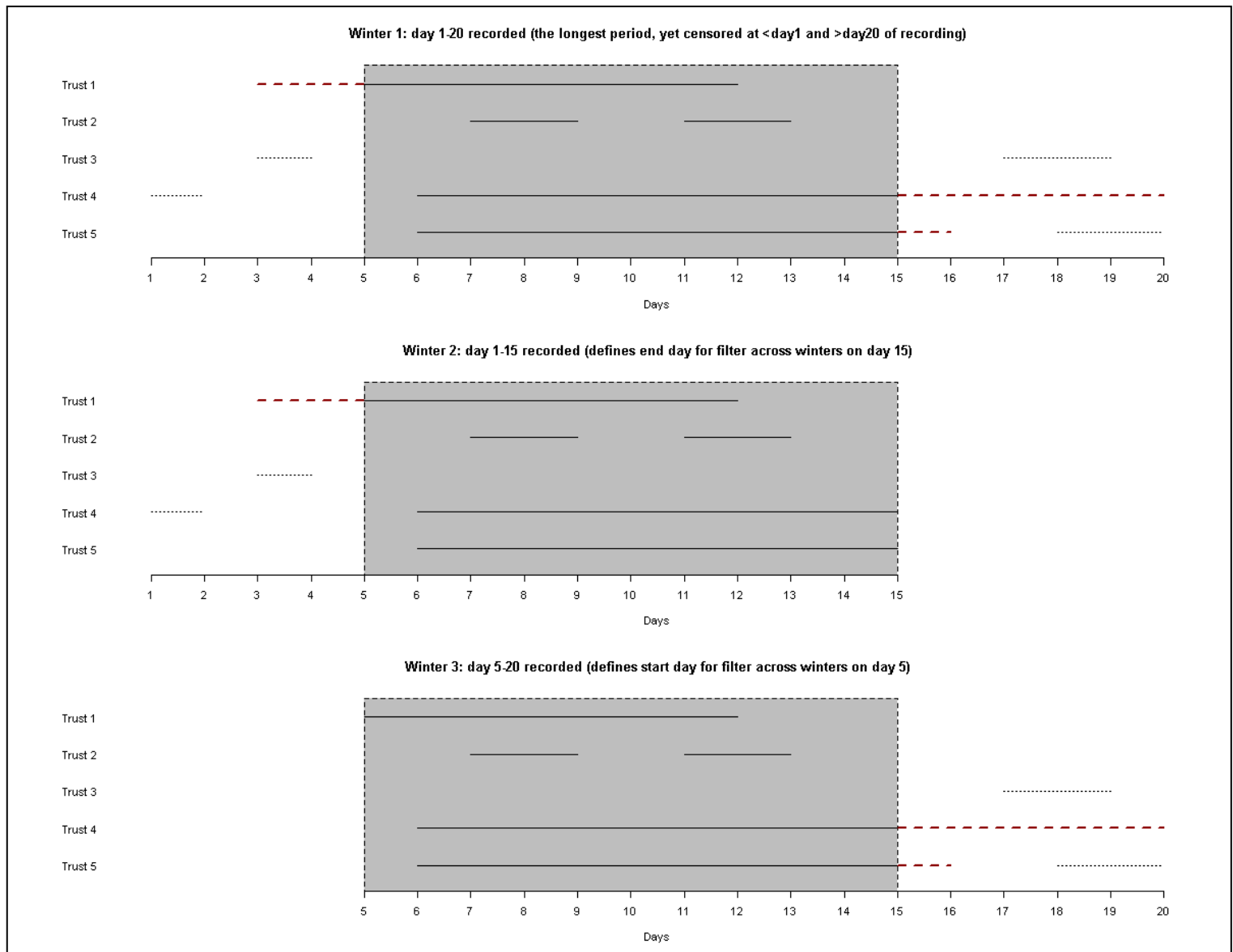
3.9 SUPPLEMENTARY MATERIAL

3.9.1 Scenario analysis for the duration of bed closures (as proxy for outbreaks of infectious gastroenteritis)

For bed closures that started or stopped on the first or last day of recording, as well as on the second (to last) day to account for the ± 48 hours period, two approaches were applied: First, all these durations were removed. Second, given that more information is available on the duration of outbreaks due to truncating the raw data to an overlapping range of dates, it was possible to include the entire duration of bed closures for most seasons (other than those defining the start and end date, and durations extending to the start or end date of recording, which were still removed as censored).

Figure 8 illustrates the differences between looking at i) the entire duration of the recording periods, ii) the duration of the overlapping range of dates (truncated), and iii) the duration of the overlapping range of dates (non-truncated) with 5 Trusts for 3 winters (for simplicity the durations were kept occurring at the same days across winters), in which winter 1 recorded the longest period (1 to 20 days), winter 2 recorded only day 1 to 15 (defining the end date for the burden analysis for a fair comparison; corresponding to 20.02. of winter 2010/11 in the actual data), and winter 3 recorded only day 5 to 20 (defining the start date for the burden analysis for a fair comparison; corresponding to 30.11. of winter 2015/16 in the actual data).

Figure 8. Illustration of approaches to handle durations of bed closures at provider-level



All horizontal lines represent days with a bed closed per provider, where the black solid lines in the grey boxes represent the data for the overlapping range of dates in all three hypothetical winters, the black dashed lines represent the data outside the overlapping range of dates, and the red dashed line the data that could potentially be considered when looking at the overlapping range of dates.

When looking at the recording periods (i.e. all vertical lines in Figure 8 irrespective of colour and shape), durations vary due to different length and timing of recording each winter. When looking at the durations of the overlapping range of dates (i.e., all vertical lines in the grey box in Figure 8), information on the actual duration is lost for e.g. Trust 1 and Trust 5. Moreover, these durations appear as censored now (as they reach the start or end date of the period), but removing them would bias results by eliminating the

longest-lasting durations, for which the entire length is also known at least partially (i.e. Trust 1 and Trust 5, but not Trust 4). When looking at the durations truncated at the overlapping range of dates but including those durations for which information is available (i.e., all vertical lines in the grey box plus the dashed red lines in Figure 8), the information available was considered that was otherwise ignored. Durations spanning the range of dates and for which the entire length from the recording periods are known were thus considered, while those outside of the filtered period were excluded (as no information is available on those across all winters). If one was to remove censored durations, the longest lasting durations would still be lost (cf. Trust 4 in Figure 8). In addition, information is incomplete for the winters that define the start or end date.

The results for i) the different recording periods, ii) the overlapping range of dates (with truncated durations), and iii) the overlapping range of dates (without truncated durations, where possible) are shown in Table 13. As expected, the mean and median of iii) were higher than ii), the range of iii) was identical to i), and fewer censored durations were removed as a last step in iii) than in ii).

Table 13. Number and length of duration of bed closures across seasons

Dataset	recording periods				overlapping range of dates (truncated)				overlapping range of dates (non-truncated)			
	No. of closures	Duration of closures			No. of closures	Duration of closures			No. of closures	Duration of closures		
	n (Δ)	mean (SD)	median (IQR)	min, max	n (Δ)	mean (SD)	median (IQR)	min, max	n (Δ)	mean (SD)	median (IQR)	min, max
raw data	7830	2.77 (1.63)	2 (1-5)	1, 5	5510	2.75 (1.61)	2 (1-5)	1, 5	5510	2.75 (1.61)	2 (1-5)	1, 5
best case	4240 (-3590)	6.89 (10.7)	3 (1-8)	1, 147	2960 (-2550)	7.02 (10.1)	3 (1-8)	1, 83	2960 (-2550)	8.12 (12.3)	4 (1-9)	1, 147
worst case	4240 (-3590)	8.09 (10.8)	5 (3-9)	1, 147	3000 (-2510)	8.16 (10.1)	5 (3-10)	1, 83	3000 (-2510)	9.38 (12.2)	5 (3-11)	1, 147
best case: no single beds ^a	4060 (-180)	7.14 (10.9)	3 (1-8)	1, 147	2850 (-110)	7.25 (10.2)	3 (1-8)	1, 83	2850 (-110)	8.39 (12.4)	4 (1-10)	1, 147
worst case: no single beds ^a	4170 (-70)	8.21 (10.8)	5 (3-10)	1, 147	2960 (-40)	8.26 (10.1)	5 (3-10)	1, 83	2960 (-40)	9.49 (12.3)	5 (3-11)	1, 147
best case: connect 48h ^b	3630 (-430)	8.12 (11.9)	4 (2-9)	1, 147	2540 (-310)	8.25 (11.1)	4 (2-10)	1, 83	2540 (-310)	9.52 (13.5)	4 (2-11)	1, 147
worst case: connect 48h ^b	3260 (-910)	10.8 (13.9)	6 (3-13)	1, 147	2300 (-660)	10.9 (12.8)	6 (3-13)	1, 83	2300 (-660)	12.5 (15.3)	7 (4-15)	1, 147
best case: no censored ^c	3130 (-500)	7.03 (9.0)	4 (2-9)	1, 75	2020 (-520)	6.71 (8.2)	4 (2-9)	1, 61	2360 (-180)	7.97 (9.9)	4 (2-10)	1, 75
worst case: no censored ^c	2740 (-520)	9.45 (10.4)	6 (3-12)	1, 88	1710 (-590)	9.09 (9.3)	6 (3-12)	1, 73	2100 (-200)	10.6 (11.3)	6 (3-13)	1, 88

Δ : change (absolute numbers), IQR: interquartile region, SD: standard deviation

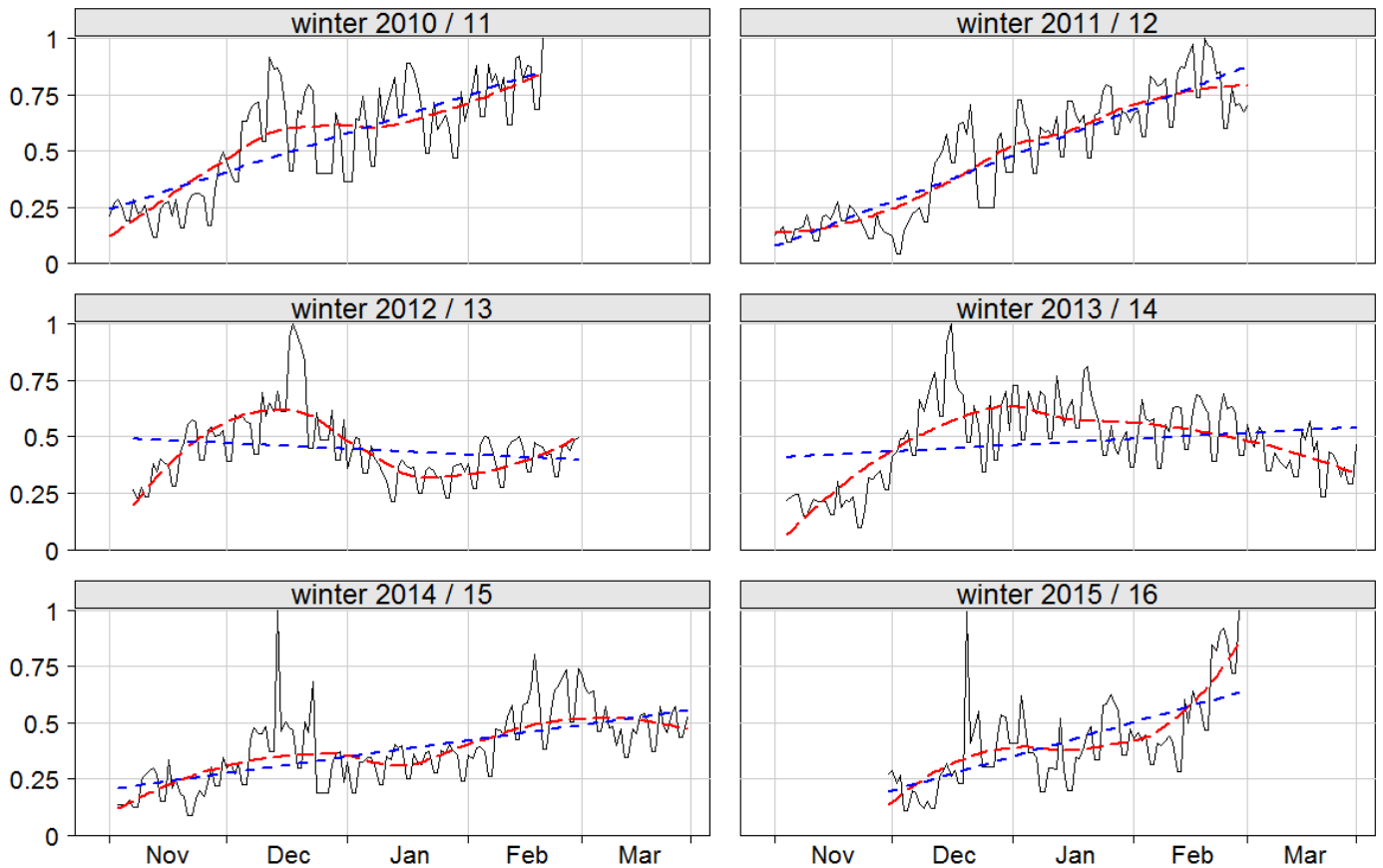
a: Removed isolated single beds closed when no other bed closure occurred within 48h.

b: Connected bed closures occurring within 48 hours.

c: Removed censored sequences of bed closures (on first or last day of recording, or second (to last) day of recording).

3.9.2 Figure of data scaled to the highest daily number per winter to identify within-winter variation

Figure 9. Time series of the observed number (data including lowest imputations) of hospital beds closed due to diarrhoea and vomiting in England per winter, 2010/11 to 2015/16 (different recording periods).



Values scaled to the highest number recorded each winter. Black line represents the data, blue dashed line the linear fit, and red long-dashed line the locally weighted regression fit.

3.9.3 Potential impact of the unknown patients' movements

In the absence of individual patient-level data the recordings of NHS England do not capture patients' movements. It is thus conceivable that a number of occupied beds were unavailable on Friday but over the weekend patients might have been discharged, which would convert these occupied beds to unoccupied beds (unavailable or not).

To illustrate the first situation of unavailable occupied beds becoming unavailable unoccupied beds, let us assume a total of 50 beds are unavailable on a Thursday, of which 20% are unoccupied (Table 14). When discharging e.g. 10 patients between Thursday to Sunday, 10 occupied beds would change to 10 unoccupied beds, and the proportion of unoccupied beds that are unavailable on Sundays should thus increase from 20% to 40% (in case they cannot be reopened altogether, i.e. the total number of beds unavailable remains constant at 50).

Table 14. Number of beds unavailable due to norovirus-like symptoms before and after weekends; theoretical example with constant total number of beds unavailable

statistic	Thursdays	Sundays	change
Beds unavailable occupied	40	30	-10
Beds unavailable unoccupied	10	20	+10
Total number of beds unavailable	50	50	0
Proportion unoccupied/occupied beds unavailable	0.250	0.667	+167%
Proportion unoccupied on <i>all</i> beds unavailable	0.200	0.400	+100%

However, it may also be that the unavailable unoccupied beds become available again for new admissions (i.e., reopening beds), reducing the total number of beds unavailable. In such a situation, when discharging again e.g. 10 patients between Thursday to Sunday and re-opening the 10 beds for new admissions, the proportion of unoccupied beds that are unavailable on Sundays should thus increase from 20% to 25% (assuming no other unoccupied beds are reopened; Table 15).

Table 15. Number of beds unavailable due to norovirus-like symptoms before and after weekends; theoretical example without constant total number of beds unavailable

statistic	Thursdays	Sundays	change
Beds unavailable occupied	40	30	-10
Beds unavailable unoccupied	10	10	0
Total number of beds unavailable	50	40	-10
Proportion unoccupied/occupied beds unavailable	0.250	0.333	+33%
Proportion unoccupied on <i>all</i> beds unavailable	0.200	0.250	+25%

In order for the proportion of beds unoccupied to stay at the expected 20% seen in the data, an additional 2.5 beds unavailable unoccupied need to be reopened, too, for the proportions to stay at the expected 20% of beds unoccupied (i.e., $7.5/37.5=0.20$).

In the actual dataset both proportions decreased; however, this seemed to be caused by an increase in the number of occupied beds unavailable, which drove the total number of all beds unavailable upwards (Table 16). At the same time, unoccupied beds may indeed have become available again (i.e., less of them were “closed” on Sundays).

Table 16. Number of beds unavailable before and after weekends, aggregated data for England, winters 2010/11–2015/16

Statistic	Thursdays	Sundays	change	signif.
Unavailable beds occupied: median (IQR)	864 (627-1200)	972 (690-1340)	+108	$P=.002$
Unavailable beds unoccupied: median (IQR)	226 (153-336)	212 (154-347)	-14	$P=.4$
Total number of beds: median (IQR)	1080 (794-1560)	1210 (864-1640)	+130	$P=.008$
Proportion unoccupied/occupied beds	0.262	0.218	-16.6%	
Proportion unoccupied on <i>all</i> beds	0.209	0.175	-16.3%	

P-values determined by Wilcoxon signed-rank test.

It seems reasonable to assume that not all of these beds unavailable “due to diarrhoea and vomiting/norovirus-like symptoms”, as NHS England refers to them, are independent observations when occurring within the same Trust and given that they might be caused by infectious pathogens. Thus, when using a paired Wilcoxon test a statistically significant increase was seen in the number of beds occupied, but a non-significant decrease in the number of beds unoccupied (note: when assuming that these aggregated numbers of beds for all acute hospitals in England were in fact unavailable independently, which seems rather implausible, then none of the changes were statistically significant).

Thus, if unavailable beds are dependent on each other, then there seems to be a “weekend effect” in that more patients are occupying beds due to gastroenteritis at the end of each weekend, while the median number of beds unavailable unoccupied stayed more or less the same over weekends, which may further indicate an underlying infectious cause of symptoms.

This finding was highlighted in section 3.6.2: “Interestingly, when assuming that beds were not closed independently, the median number of beds closed occupied was higher for Sundays than for Thursdays (Wilcoxon signed-rank test: $P=.002$), while the change in beds closed unoccupied was statistically insignificant ($P=.4$). This increase in patients

occupying beds due diarrhoea and vomiting towards the end of weekends while the numbers of unoccupied beds remain constant may thus be a further indication for an underlying infectious cause.”^[251]

3.9.4 Choice of imputation strategy

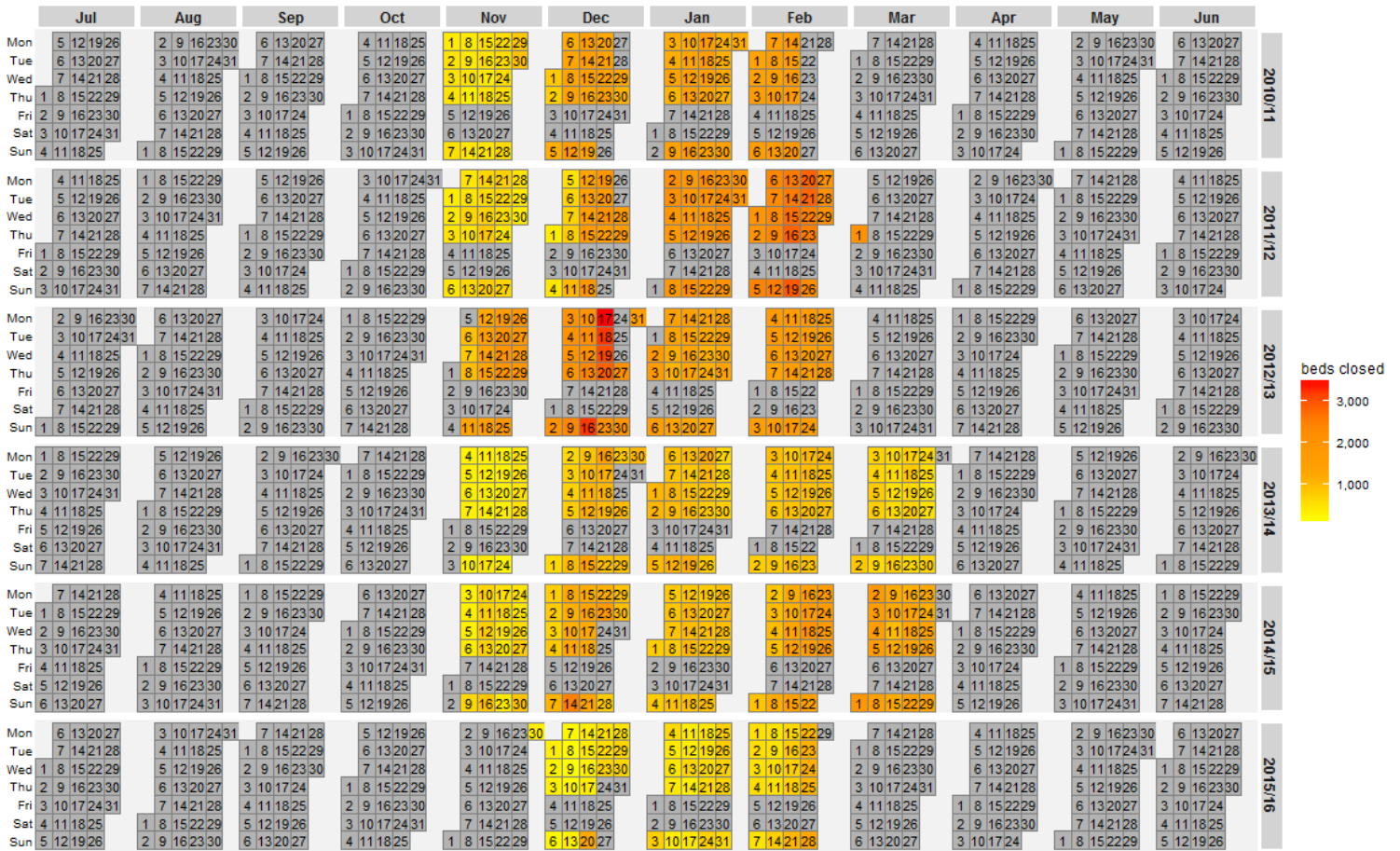
In general, missing data can be addressed with different imputation strategies for situations where a complete-case analysis (i.e., no missing values at all) or available-case analysis (i.e., no missing values for the chosen variables) are deemed insufficient.^[124,252]

Broadly speaking, the imputation strategy will differ with the cause of values missing:

- Data missing at random are characterised by the fact that, in theory, similar values should be obtainable for complete cases and missing cases except for stochastic variation.^[124] In such situations, various techniques of multiple imputation have been developed that create multiple datasets where the missing values are replaced by a range of plausible values drawn from a pre-specified distribution.^[124,253]
- For data not missing at random, the missing values are conditional on the reason of why the values are missing.^[124] For this type of missing data multiple imputation techniques likely introduce bias into the analysis.

The values in the dataset of NHS England were missing non-randomly at weekends and public/bank holidays (Figure 10). Bed-days that became unavailable due to gastroenteritis over the weekend should generally have resulted in a more conservative approach by healthcare staff.^[87] Hence, it seems likely that – at times of decreased personnel as occurring during the weekend – the bed-days would simply be kept unavailable for infection control to decrease any chance of an outbreak occurring, or for it to be sustained. This is the reason why the unconditional last-observation carried forward (LOCF) was considered; this method carries forward the value on Thursdays to inform the missing values for Fridays and Saturdays.

Figure 10. Aggregated daily number of all hospital beds unavailable due to diarrhoea and vomiting in England, winters 2010/11 to 2015/16 (data from NHS England).



However, it may have also been possible that some hospitals discharged patients who felt well enough, e.g. to free much needed beds during times of increased demand and reduced supply. Then, the number of bed-days unavailable on a Sunday may be lower than those on a Monday. Thus, in order to capture what had been going on over the weekend if an unavailable bed was first recorded on a Sunday but not on the preceding Thursday, an unconditional first-observation carried backward (NOCB) was considered where the value of Sundays was carried backwards to impute values for Saturdays and Fridays.

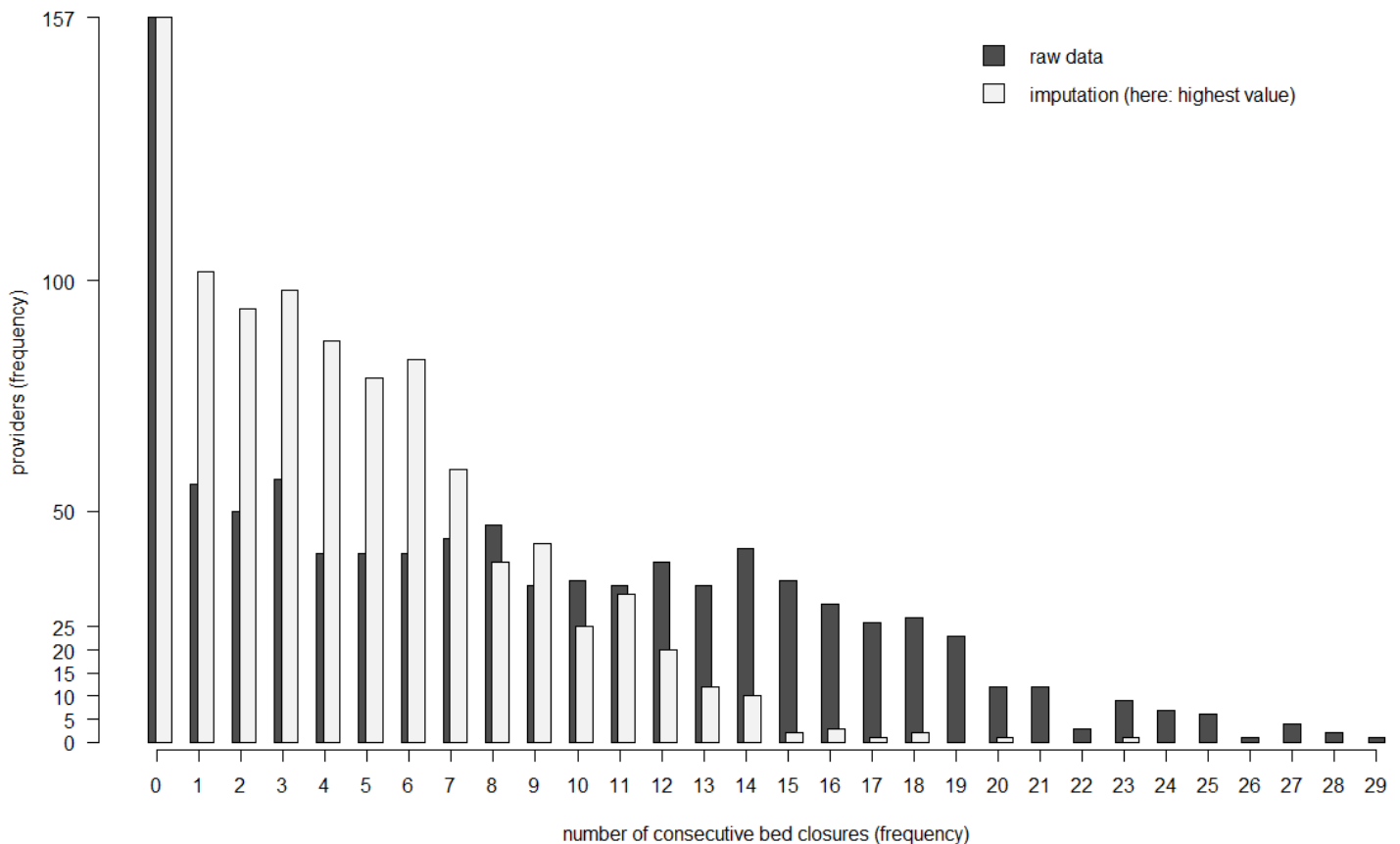
However, in order to not bias values systematically upwards, two scenarios were considered: The conservative best-case scenario considered the lowest value imputed with either LOCF or NOCB. Thereby, the imputation was effectively conditional on unavailable beds being recorded before and after the missing values; otherwise, the missing values would reflect that there was no unavailable bed recorded either before or

after, or a lower number of beds. Conversely, the highest value imputed with either LOCF or NOCB was considered in a worst-case scenario, thus unconditional of the number of unavailable beds before and after the missing values.

Overall, neither LOCF nor NOCB was used in isolation, which would have resulted in lower values than the worst-case scenario. Instead, a new dataset was created for both the best-case and worst-case scenario from the two datasets containing imputed values with LOCF and NOCB.

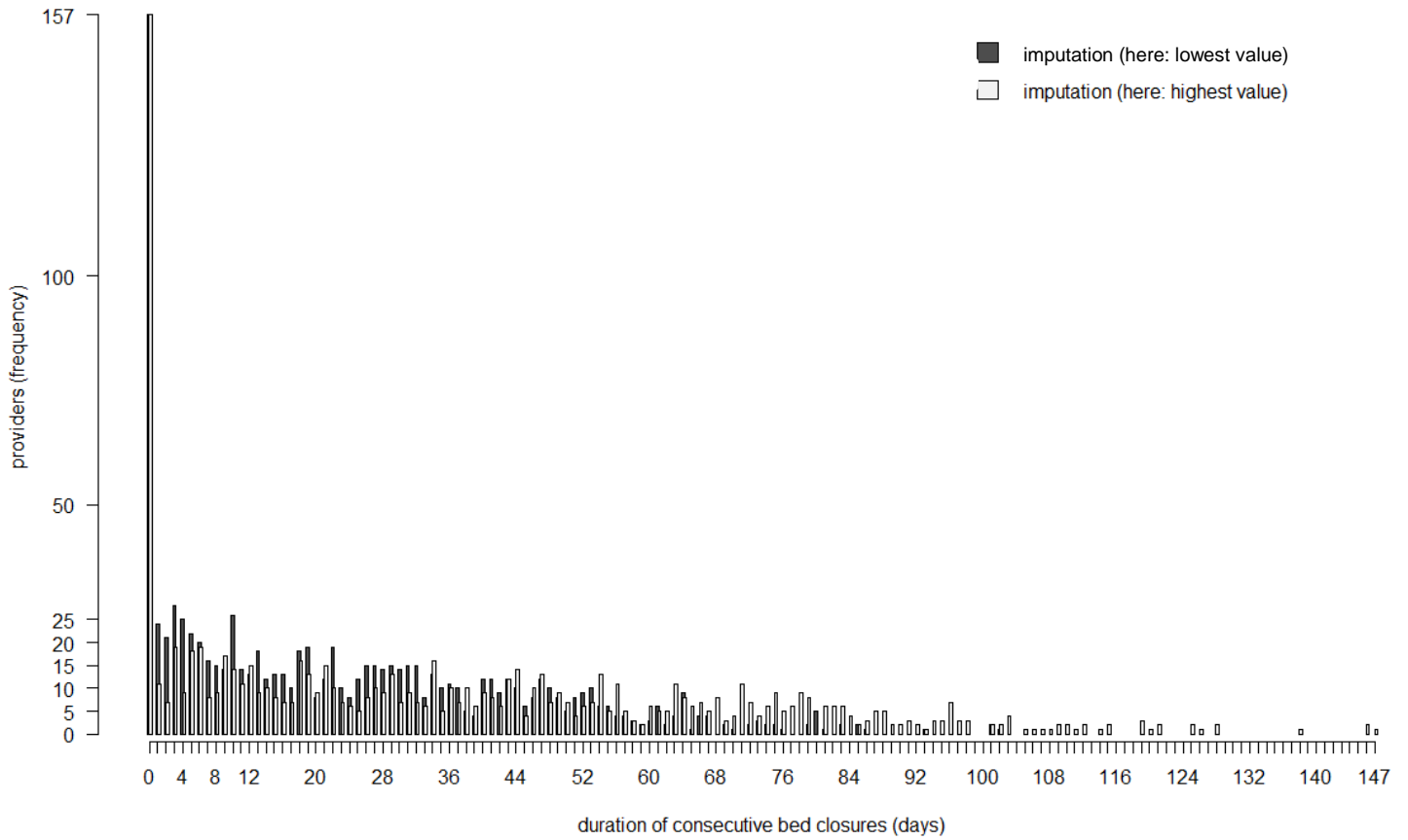
Moreover, missing values were imputed at the provider-level to allow accurate analysis of the dataset. Otherwise, the missing data at weekends and public/bank holidays would represent a third of all values, and thus would have biased the analysis by overestimating the number of bed closures per provider (Figure 11) and underestimating the duration of bed closures due to only recording a maximum of five consecutive days (Sundays to Thursdays).

Figure 11. Frequency of acute care hospital beds being unavailable due to diarrhoea and vomiting in England across winters, 2010/11 to 2015/16.



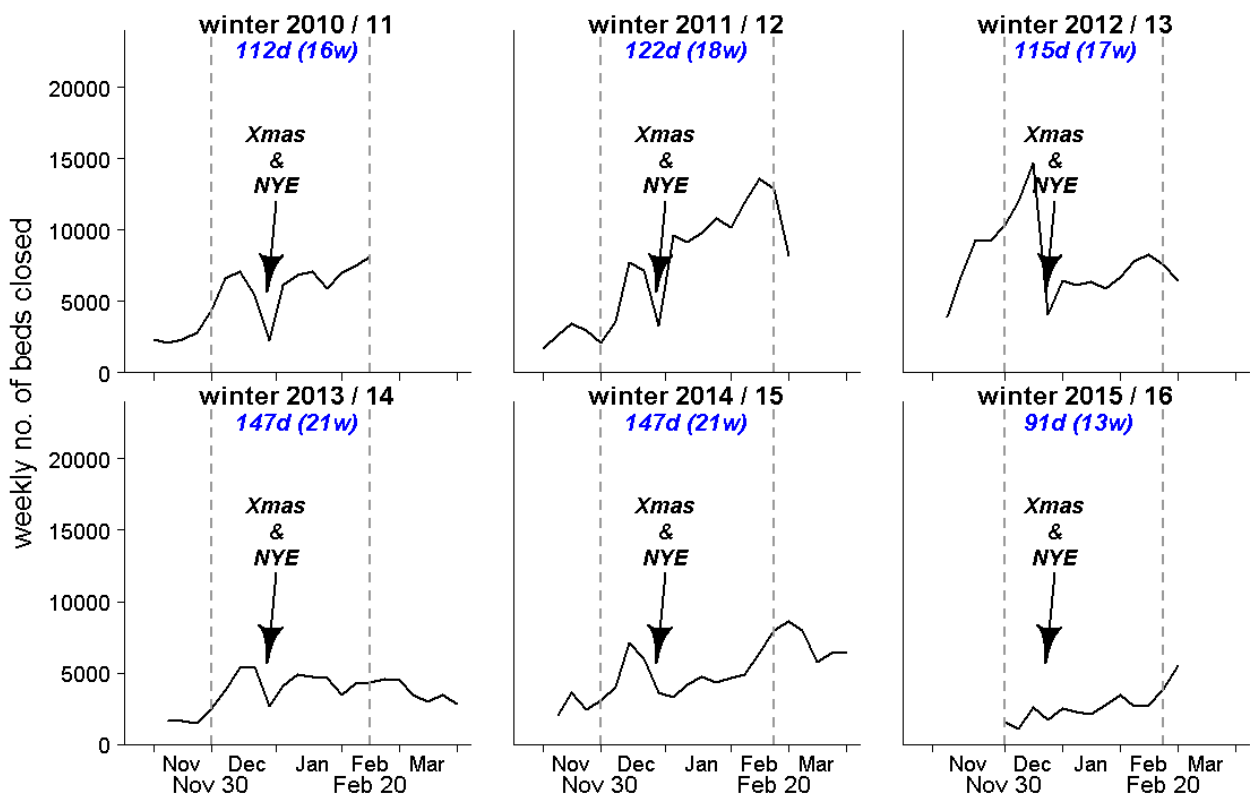
Even with imputations, the variation in bed-day closure duration was high (Figure 12), with a few providers having to deal with bed closures for the entire duration of recording.

Figure 12. Duration of consecutive days that acute care hospital beds were unavailable due to diarrhoea and vomiting in England across winters, 2010/11 to 2015/16.



Lastly, observations were filtered to the same range of days that were available for all six winters in order to enable a fair comparison (Figure 13). This was done only after the imputation to capture the impact also for the first and last day of recording.

Figure 13. Weekly number of all hospital beds unavailable due to diarrhoea and vomiting in England, winters 2010/11 to 2015/16 (data from NHS England).



3.9.5 Impact of imputations on descriptive statistics

Generally, using an imputation strategy will inevitably affect the variation.^[124] In order to investigate the extent of the impact of the imputations on the descriptive statistics reported in the paper, the central tendencies (mean, median) and measures of spread (SD, IQR) were compared for the raw data and the imputations of the daily number of all occupied and unoccupied beds unavailable (Table 17).

Table 17. Comparing the central tendencies and measures of spread in the raw data and in both imputations for the daily number of all beds unavailable in England, winters 2010/11–2015/16.

statistic	raw data (NHS England)	lowest imputation	highest imputation
mean	1,227	1,100 (-10.4%)	1,382 (+12.6%)
SD	607	586	688
median	1,141	982 (-13.9%)	1,251 (+9.6%)
IQR (Q1-Q3)	794-1,580	689-1,435	886-1,800

IQR: interquartile range, NHS: National Health Service, Q1: lower quartile, Q3: upper quartile, SD: standard deviation.

Overall, the lowest imputation underestimated both central tendencies and measures of spread of the raw data, while the highest imputation overestimated it (Table 17). This finding was included in section 3.6.2: “Furthermore, when comparing central tendencies (mean, median) and measures of spread (SD, IQR) for the daily number of beds closed between the raw data and the imputations, the lowest imputation underestimated both central tendencies and measures of spread of the raw data while the highest imputation overestimated it (data not shown).”^[251] Note: The data are shown here now (Table 17).

The median of the highest imputation is closer to the median of the raw data though, and instead of reducing the variation of values, a common issue with imputation strategies due to relying on the existing observations,^[124] the highest imputation did in fact increase the variation. This finding provides some indication that, by being broader, the highest imputation may be closer to capturing the (unknown) actual number. The text in section 3.6.2 concluded more conservatively: “With the information available, it is not possible to determine where exactly the number of beds closed lies on the range of the lowest to highest imputations; this inaccuracy is unavoidable though due to the values missing.”^[251]

3.9.6 Validation of imputation strategies

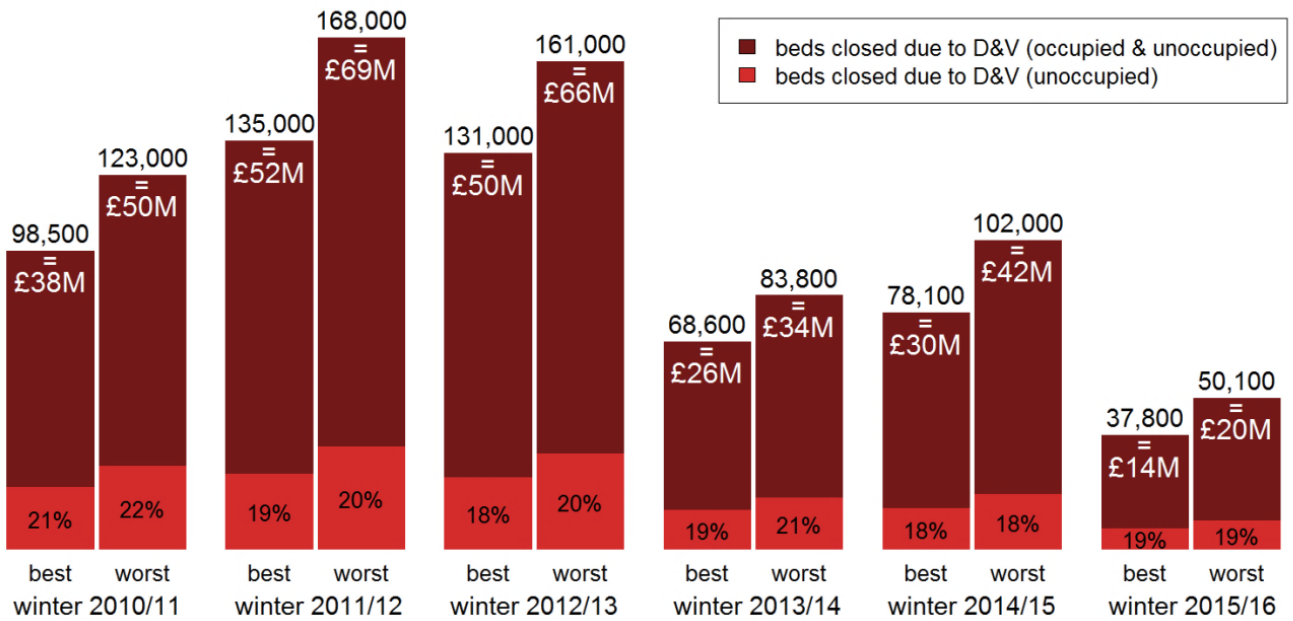
Since publishing the paper that underlies chapter 3, additional data have become available and NHS England has changed the data collection to include daily observations. Thus, contrary to the previous winters since inception of the data collecting scheme in 2010/2011, unavailable bed-days were recorded during weekends and public/bank holidays, too.^[52] Between 01 December 2016 and 19 February 2017, 58,773 bed-days in total were unavailable due to gastroenteritis.

This change in data collection provided a unique opportunity to validate the imputation strategies against the actual number recorded. First, all observations for weekends and public/bank holidays in winter 2016/2017 were deleted from the dataset to resemble the situation of the data in the previous six winters. Second, the algorithm of the imputation strategies was re-run to obtain best-to-worst case scenario estimates.

As a result, the lowest-to-highest imputations led to 51,600-69,100 unavailable bed-days in total in winter 2016/17. The difference to the actual number of 58,773 bed-days recorded was thus smaller for the lower estimate (with -12.2% and +17.6% for the lowest and highest imputation, respectively). When combining the two imputations, their average 60,350 bed-days were 2.6% higher than the actually recorded value.

This result seems to suggest that the actual number of recorded observations may be found around the average of the two best-to-worst case imputation strategies (cf. Figure 14). However, potential reporting variations on weekends and public/bank holidays are not taken into account despite that some hospitals will not have sufficient infection control services available on those days.

Figure 14. Number of unavailable bed-days and expenditures due to diarrhoea and vomiting in England, winters 2010/11-2015/16.



4 FINANCIAL EXPENDITURES VS. OPPORTUNITY COSTS: HOSPITAL BURDEN OF NOROVIRUS

Previously, chapter 3 illustrated the burden of unavailable bed-days due to norovirus-associated gastroenteritis in hospitals, which is a particularly pressing concern during winter. The chapter also costed the burden conventionally, using as input the number of bed-days as well as a proxy for staff absence episodes. Owing to data unavailability, however, the study ignored the actual number of inpatients occupying beds, and their potential stay in hospital regardless of gastroenteritis (i.e., they may have stayed a few days longer anyway due to the underlying primary medical condition for which they were initially admitted to hospital).

Thus, chapter 4 aims to estimate the hospital burden of norovirus by looking at actual patients and by considering their excess length of stay. Moreover, the time horizon is widened to an annual period to reflect that norovirus outbreaks occur throughout the year, even though they are a particularly stressing concern during winter. Nonetheless, opportunity costs for alternative admissions forgone arise regardless of the time of the year, and only depend on the steady demand for beds and an insufficient number of beds supplied in hospitals. Chapter 4 thus estimates the annual hospital burden of norovirus in England, and contrasts the conventional costing approach of using financial expenditures with the opportunity costs from forgone admissions.

Title of paper, name of authors and affiliations:

Estimating the hospital burden of norovirus-associated gastroenteritis in
England and its opportunity costs for non-admitted patients.

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- 8 *University College Hospitals London, Infection Control office, London, United Kingdom*
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Publication status: submitted (under review). Additional unpublished material is presented in section 4.11.

4.1 COVER SHEET OF RESEARCH PAPER 3

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SECTION A – Student Details

Student	Frank Sandmann
Principal Supervisor	Prof. Mark Jit
Thesis Title	The true cost of epidemic and outbreak diseases in hospitals

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Clinical Infectious Diseases
Please list the paper's authors in the intended authorship order:	FG Sandmann (me), L Shallcross (collaborator at UCL), N Adams (collaborator at PHE), DJ Allen (collaborator at PHE/LSHTM), PG Coen (collaborator at UCL), A Jeanes (collaborator at UCL), Z Kozlakidis (collaborator at UCL), L Larkin (collaborator at PHE), F Wurie (collaborator at UCL), JV Robotham (associate supervisor), M Jit (main supervisor), SR Deeny (associate supervisor).
Stage of publication	Undergoing revision

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall methodology, extracted the hospital episodes statistics data, performed the analysis, interpreted results,
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	and drafted the paper and subsequent revisions during the peer-review. JVR, MJ, and SRD equally provided critical comments on the methodology, analysis, interpretation of results, and the different versions of the paper. MJ, JVR, SRD and I conceived the study. Collaborators at UCL (LS, PGC, AJ, ZK, FW) provided local hospital outbreak data. Collaborators at PHE (NA, DJA, LL) provided national surveillance data of enteric laboratory reports/cases and national hospital outbreak data. All authors commented critically on the interpretation of results and the different versions of the paper. I gave a presentation of this study at PHE's Gastrointestinal Department seminar series (London, 2017).
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Student Signature: _____

Date: 27.01.2018

Supervisor Signature: _____

Date: 27.01.2018

4.2 ABSTRACT

Background. Norovirus places a substantial burden on healthcare systems, arising from infected patients, disease outbreaks, beds kept unoccupied for infection control, and staff absences due to infection. In settings with high rates of bed occupancy, opportunity costs arise from patients who cannot be admitted due to beds being unavailable. With several treatments and vaccines against norovirus in development, quantifying the expected economic burden is timely.

Methods. The number of inpatients with norovirus-associated gastroenteritis in England were modelled using infectious and non-infectious gastrointestinal Hospital Episode Statistics codes and laboratory reports of gastrointestinal pathogens collected at Public Health England. The excess length of stay from norovirus was estimated with a multi-state model and local outbreak data. Unoccupied bed-days and staff absences were estimated from national outbreak surveillance. The burden was valued conventionally using accounting expenditures and wages, which was contrasted to the opportunity costs from forgone patients using a novel methodology.

Results. Between July 2013 and June 2016, 17.7% (95%-confidence interval: 15.6%–21.6%) of primary and 23.8% (20.6%–29.9%) of secondary gastrointestinal diagnoses were norovirus-attributable. Annually, the estimated median 290,000 (interquartile range: 282,000–297,000) occupied and unoccupied bed-days used for norovirus displaced 57,800 patients. Conventional costs for the National Health Service reached £107.6 million; the economic burden approximated to £297.7 million and a loss of 6,300 quality-adjusted life years annually.

Conclusions. In England, norovirus is now the second-largest contributor of the gastrointestinal hospital burden. With the projected impact being greater than previously estimated, improved capture of relevant opportunity costs seems imperative for diseases like norovirus.

4.3 INTRODUCTION

Norovirus has been associated with almost one-fifth of cases of all-cause acute gastroenteritis worldwide,^[49] resulting in an estimated median 698.8 million illnesses and 218,800 deaths annually across all ages.^[55] Norovirus most commonly occurs in the community,^[55,254] with relatively short-lived symptoms in healthy individuals, which are currently managed with supportive therapies such as rehydration.^[58] However, symptoms can be more serious in the very young, frail, or elderly and local outbreaks of norovirus occur frequently, which are highly disruptive and have significant economic cost particularly in hospitals internationally.^[41,255-257] These outbreaks can lead to increased norovirus-specific hospital admissions and subsequently nosocomial infections that may reduce available beds within the hospital system through infected patients blocking space for new admissions, beds left unoccupied for reasons of infection control and to allow cleaning and decontamination after outbreaks, and staff absences due to infection.^[41,107,258]

The impact of norovirus on the hospital system prompted the introduction of the English Hospital Norovirus Outbreak Reporting System (HNORS) in 2009,^[259] and in 2010 the National Health Service (NHS) England started monitoring the performance of all acute care hospitals during winter.^[52] While both systems enable detection of hospital bed pressures and norovirus outbreaks, neither collects individual-patient data. Therefore, the data collected by such surveillance systems alone do not capture the full burden of norovirus. With several antiviral treatments and vaccine candidates in development,^[56,95] obtaining a comprehensive overview of the baseline burden of norovirus in hospitals is timely to inform policy makers and investment in control strategies.

Moreover, as hospitals in many countries,^[6] including England,^[7] face high occupancy rates of beds, patients who cannot be admitted due to beds being unavailable result in health and economic losses to the healthcare system. Costing the burden of hospital infections like norovirus has previously only considered actual expenditures incurred from dealing with an outbreak,^[41,258] ignoring the wider health impact for other patients awaiting admission.^[260] This is likely to underestimate the impact of norovirus on the healthcare systems and, consequently, any benefits from investing in novel vaccines, treatments or infection control.

4.4 METHODS

4.4.1 Data sources

4.4.1.1 Number of patients, bed-days lost, and staff absences during norovirus outbreaks

Since 2009, hospitals have been encouraged to voluntarily report norovirus outbreaks (defined as two or more cases in a functional care unit) to HNORS at <http://bioinformatics.phe.org.uk/noroOBK>. Previously, the under-reporting in this web-based surveillance system was estimated at about 20%.^[259] The number of patients, staff absences, and lost bed-days due to norovirus were obtained for all outbreaks declared over between July 2009 and by week 27, 2016.

4.4.1.2 Hospital statistics for gastrointestinal illnesses

The observed number of inpatients with primary and secondary gastrointestinal disease diagnoses, and the bed-days occupied by the inpatients with primary diagnoses, were obtained for July 2009 to June 2016 from the Hospital Episode Statistics (HES) database, which holds all records of NHS hospitalisations in England.^[244] Primary diagnoses describe the main reason for hospitalisation, while secondary diagnoses describe co-morbidities of patients treated for another primary medical reason. Cases with all-cause gastroenteritis were identified using the *International Classification of Diseases, version 10* (ICD10), and the diagnosis codes of infectious as well as non-infectious intestinal diseases A00–A09, K52.8 and K52.9.^[115,116]

4.4.1.3 Laboratory data of gastrointestinal pathogens

The weekly number of laboratory reports submitted to Public Health England for surveillance purposes by microbiology laboratories across England were obtained for July 2009 to June 2016 for the following gastrointestinal pathogens: adenovirus (enteric infections-associated Group F serotypes 40 and 41), astrovirus, *Campylobacter*, *Cryptosporidium*, *Giardia*, norovirus, rotavirus, non-typhoidal *Salmonella* (i.e. excluding *S. typhi* and *S. paratyphi*), and *Shigella*. *Listeria* cases were obtained from national surveillance of listeriosis in England and Wales. In a separate analysis, cases of

shiga toxin-producing *Escherichia coli* (STEC) were also included as this was only available up to December 2015.

4.4.1.4 Patient-level data of norovirus infections from a local hospital

This study obtained individual-level data collected during a norovirus outbreak on four wards of a large teaching hospital in London in 2015. A research nurse visited affected wards daily to collect information on new cases, bed closures and to map the movement of patients between wards. Routinely collected data were also obtained on age, sex, dates of admission and discharge, primary and up to 11 secondary diagnosis codes, norovirus sample collection date, and discharge status for all patients admitted to the same wards and days for 2015 with a two-year look-back. For an additional two weeks before and after the outbreak, i.e. 43 days in total each year, data were captured on the infection status with norovirus genogroup II (GII). Cases were identified based on the primary diagnosis code, the first positive norovirus GII infection sample during the hospital stay and, for the outbreak in 2015, symptom onset.

4.4.1.5 Number of bed-days kept unoccupied due to norovirus-like symptoms during winters

It is mandatory for acute care hospitals to report the number of bed-days kept unoccupied due to diarrhoea and vomiting/norovirus-like symptoms during winters to NHS England since 2010. These data were obtained for winters 2010/11 to 2015/16.^[52]

For more details on data sources and information retrieval, see Supplementary Material 4.10.1.

4.4.2 Statistical analysis to estimate the burden of disease

4.4.2.1 Linear regression models

Multiple linear regression models were used to attribute norovirus to patients with gastroenteritis by using the laboratory reports of relevant gastrointestinal pathogens as explanatory variables and inpatients diagnosed with gastrointestinal illnesses as the response variable (Supplementary Material 4.10.2). In a separate analysis, the data were limited up to December 2015 to be able to include STEC.

4.4.2.2 Multi-state models

The excess length of hospital stays due to norovirus were estimated with a multi-state model that consisted of four mutually-exclusive states: (1) admitted (uninfected), (2) infected/diseased, (3) discharged alive, and (4) in-hospital death (Supplementary Material 4.10.3). After admission (1), all inpatients were discharged alive (3) or died (4); becoming infected/diseased (2) was optional before being discharged alive (3) or dead (4), too. The model used the empirical transition matrix of inpatients from the local patient-level hospital data. The model was run separately with all norovirus cases, and for cases with a secondary norovirus diagnosis.

4.4.2.3 Adjustments for potential under-reporting of unoccupied bed-days and staff absences

The number of bed-days kept unoccupied during norovirus outbreaks was estimated based on the national surveillance data. As these data are voluntarily reported there could be under-reporting of outbreaks, or lost bed-days. Under-reporting of lost bed-days during an outbreak (and implicitly under-reported outbreaks) was accounted for using the recorded number of unoccupied bed-days mandatorily reported to NHS England (Supplementary Material 4.10.4). The reported number of staff absences was adjusted by the estimated under-reporting of outbreaks^[259] and by using a previous norovirus outbreak study in England^[41] (Supplementary Material 4.10.5).

All analyses were performed in R version 3.3.1.^[261] For the multi-state model, the R-package *mvna* was used to model the hazards between states^[262] and *etm* to estimate the excess length of stay.^[263] The median and interquartile range (IQR) are reported across seasons; for results per season see Supplementary Material 4.10.1 and 4.10.8.

4.4.3 Costing the burden of disease

4.4.3.1 Costing convention

For inpatients with norovirus-associated gastroenteritis and bed-days kept unoccupied, expenditures were calculated conventionally using national administrative accounting data for 2015/16^[243] (Supplementary Material 4.10.6). Staff absences due to infection were costed based on the national average wage of nurses in 2015/16.^[264] In order to

indicate financial (monetary) savings on non-fixed hospital resources if all norovirus cases were to be averted,^[265] a proportion of variable costs of 15% was assumed of the total healthcare expenditure on norovirus, including staff absence costs.^[266]

4.4.3.2 Opportunity costing from forgone admissions

Given the high occupancy rates of hospital beds in England,^[7] opportunity costs arise from alternative patients who cannot be admitted due to beds being unavailable, which can be expressed particularly in terms of their forgone net benefit, i.e. the health gain minus expenditure.^[260] For the expenditure incurred when hospitalised, the activity-weighted mean expenditure of non-gastroenteritis cases was considered.^[243] The expected health gain from hospital treatment was estimated in terms of quality-adjusted life years, QALYs, using the local patient sample (Supplementary Material 4.10.7). Three sub-groups of patients were distinguished with a) acute life-threatening conditions, b) chronic conditions, and c) none of these conditions. QALY-gains beyond one year were discounted at 3.5%, and £20,000 was considered as monetary value assigned to each QALY gained.^[267] In case a higher net benefit was achievable with the alternative patients forgone, the sum of the incurred expenditure and the forgone net benefit approximate to opportunity costs.^[260]

4.4.3.3 Sensitivity analysis

Multivariate sensitivity analyses were performed on all input parameters (Supplementary Table 28).

4.4.4 Ethics approval

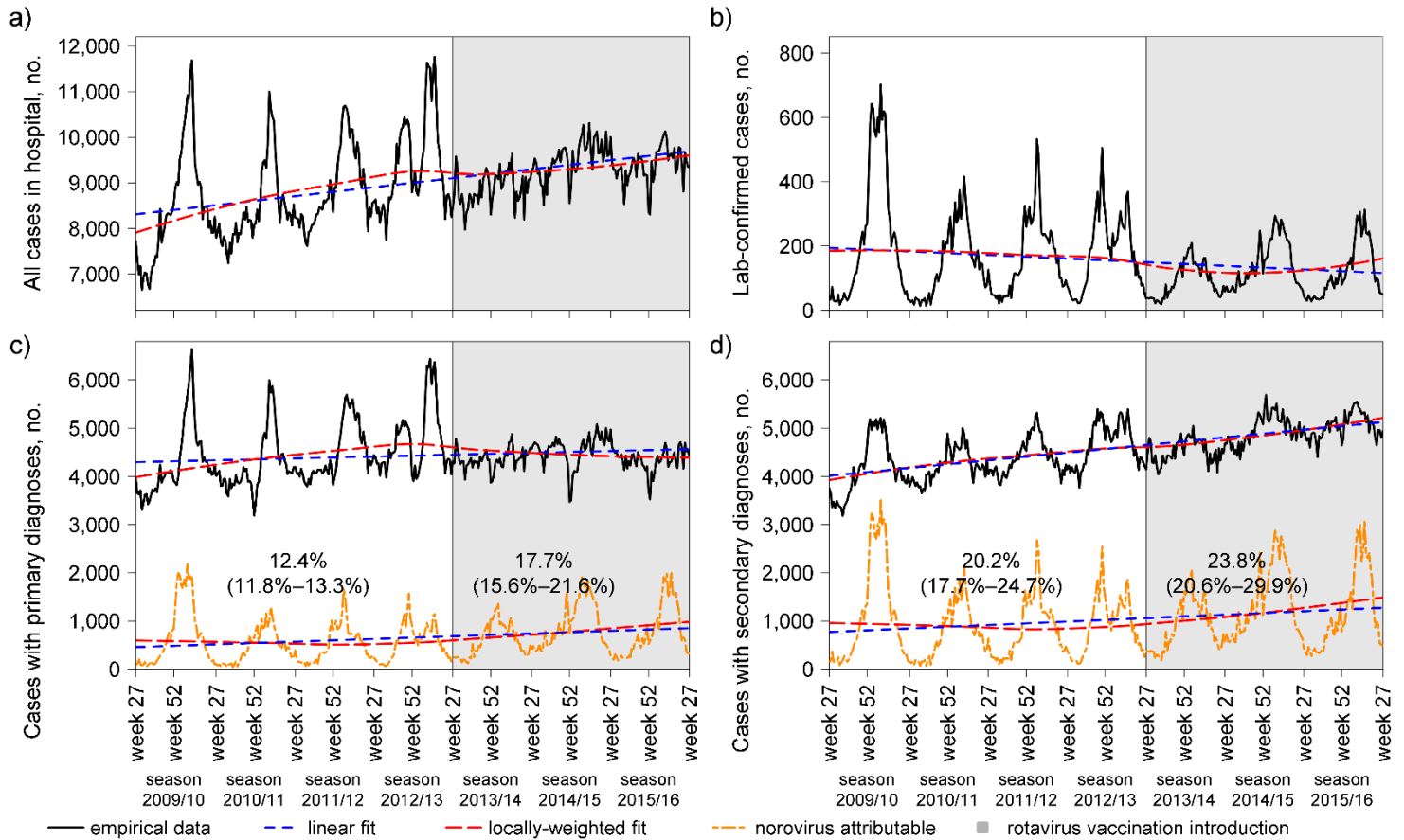
Ethical approvals for this study were received from the Ethics Committee of the London School of Hygiene & Tropical Medicine (reference number: 11824) and the North West - Liverpool Central Research Ethics Committee (REC reference: 14/NW/1433).

4.5 RESULTS

4.5.1 Description of the data

During July 2009 to June 2016, there were a total of 8,140 norovirus outbreaks voluntarily reported to HNORS, involving 77,800 patients, 20,100 staff recorded absent and 99,200 lost bed-days (Supplementary Table 20). Of the 658,100 enteric laboratory reports in total to national surveillance, the three most frequently reported pathogens were *Campylobacter* with 60.7%, rotavirus with 10.8%, and norovirus with 8.6%. Concurrently, HES recorded across all ages 1,621,000 primary all-cause gastrointestinal diagnoses vs. 1,672,000 patients with secondary all-cause gastrointestinal diagnoses (including 13.1% day cases). The number of primary gastrointestinal diagnoses stabilised after July 2013, while the number of patients with secondary gastrointestinal diagnoses kept increasing (Figure 15), driven by infections in adults and the elderly (Supplementary Figure 17). Based on the data of NHS England, an estimated 142,100–186,000 unoccupied acute care hospital bed-days were closed (i.e., unavailable) due to norovirus-like symptoms during the six winters from 2010/11 to 2015/16.

Figure 15. National hospital statistics for inpatients with infectious and non-infectious gastrointestinal (primary and secondary) diagnoses and laboratory-confirmed cases of norovirus in England, July 2009 to June 2016, visualising norovirus-attributable proportions using linear regressions fitted to the data before and after July 2013.



The analysis of the local patient-level sample comprised 2,509 individual hospital stays, including 33 associated with norovirus and another 11 with primary infectious intestinal diagnoses (Table 18).

Table 18. Demographic characteristics of the local sample of patients from a teaching hospital in London, England, on the wards affected by the norovirus outbreak of May 31 to June 15, 2015, and the previous two years.

Variables	Control patients without gastroenteritis				Cases with norovirus		
	All patients analysed (cases and controls)	Patients with acute life-threatening conditions ^a	Patients with chronic conditions ^b	Patients without chronic or life-threatening conditions ^c	Suspected / confirmed norovirus infection ^d	Cases with primary iid or norovirus diagnosis ^e	Cases with secondary norovirus diagnoses
Patients, n (%)	2,509 (88.0%)	537 (18.8%)	871 (30.5%)	1,057 (37.0%)	33 (1.2%)	17 (0.6%)	27 (0.9%)
Age (years), mean (SD)	59.2 (20.2)	75.1 (14.3)	61.7 (17.6)	48.7 (18.5)	70.8 (18.2)	56.9 (23.5)	73.5 (16.6)
Sex (female), n (%)	1,265 (50.4%)	258 (48.0%)	422 (48.4%)	557 (52.7%)	21 (63.6%)	11 (64.7%)	17 (63.0%)
CCI score (>0), n (%)	1,440 (57.4%)	537 (100.0%)	871 (100.0%)	0 (0.0%)	27 (81.8%)	8 (47.1%)	24 (88.9%)
In-hospital mortality, n (%)	54 (2.2%)	21 (3.9%)	26 (3.0%)	*	*	0 (0.0%)	*
LOS (days), mean (range)	5.0 (0, 43)	7.2 (0, 43)	5.4 (0, 43)	3.3 (0, 40)	15.8 (3, 43)	5.7 (0, 25)	17.0 (3, 43)
Excess LOS (days), mean (95% CI) ^f	n/a	n/a	n/a	n/a	3.33 (0.17–6.50)	n/a	3.95 (0.35–7.55)
QALY gain (undiscounted), mean (95% CI) ^g	0.179 (0.0001, 0.386)	0.307 (0.175, 0.377)	0.313 (0.189, 0.403)	0.002 (0.00005, 0.017)	0.227 (0.003, 0.358)	0.102 (0.0004, 0.295)	0.250 (0.009, 0.365)
QALY gain (discounted), mean (95% CI) ^g	0.142 (0.0001, 0.293)	0.260 (0.162, 0.309)	0.239 (0.175, 0.308)	0.002 (0.00005, 0.017)	0.188 (0.003, 0.295)	0.078 (0.0004, 0.190)	0.211 (0.009, 0.299)

CCI: Charlson comorbidity index, CI: confidence interval, GII: norovirus genogroup II, iid: infectious intestinal disease, LOS: length of stay, n/a: not applicable, PCR: polymerase chain reaction, QALY: quality-adjusted life year, SD: standard deviation.

a: myocardial infarctions, congestive heart failures, or cerebrovascular diseases.

b: CCI > 0 but not acutely life-threatening (i.e., myocardial infarctions, congestive heart failures, or cerebrovascular diseases).

c: CCI = 0, i.e. no chronic or life-threatening conditions.

d: Suspected infection (for the norovirus outbreak cluster in 2015) and all laboratory-confirmed norovirus GII infections; partly overlapping.

e: Patients with a primary gastrointestinal diagnosis and laboratory-confirmed norovirus infection (n=6) or without confirmed norovirus infection (n=11). No excess LOS is presented here given that hospitalisations for a primary IID but without laboratory-confirmed norovirus diagnosis cannot necessarily be categorised as an excess stay.

f: Estimated with the multi-state model (Supplementary Material 4.10.3).

g: For cases with secondary norovirus diagnoses, the QALYs gained were driven by the high level of comorbidities. If one approximated the gastroenteritis-related health gain by subtracting the QALY gain of control patients from the QALY gain of inpatients with secondary norovirus diagnoses, one derives 0.211-0.142=0.069 (i.e., close to the gain of primary cases). For all cases, the activity-weighted mean (discounted) QALY gain amounted to (0.069*27+0.078*17)/44=0.072 QALYs gained, i.e. about half of the control patients who gained 0.142 QALYs (see Supplementary Table 21).

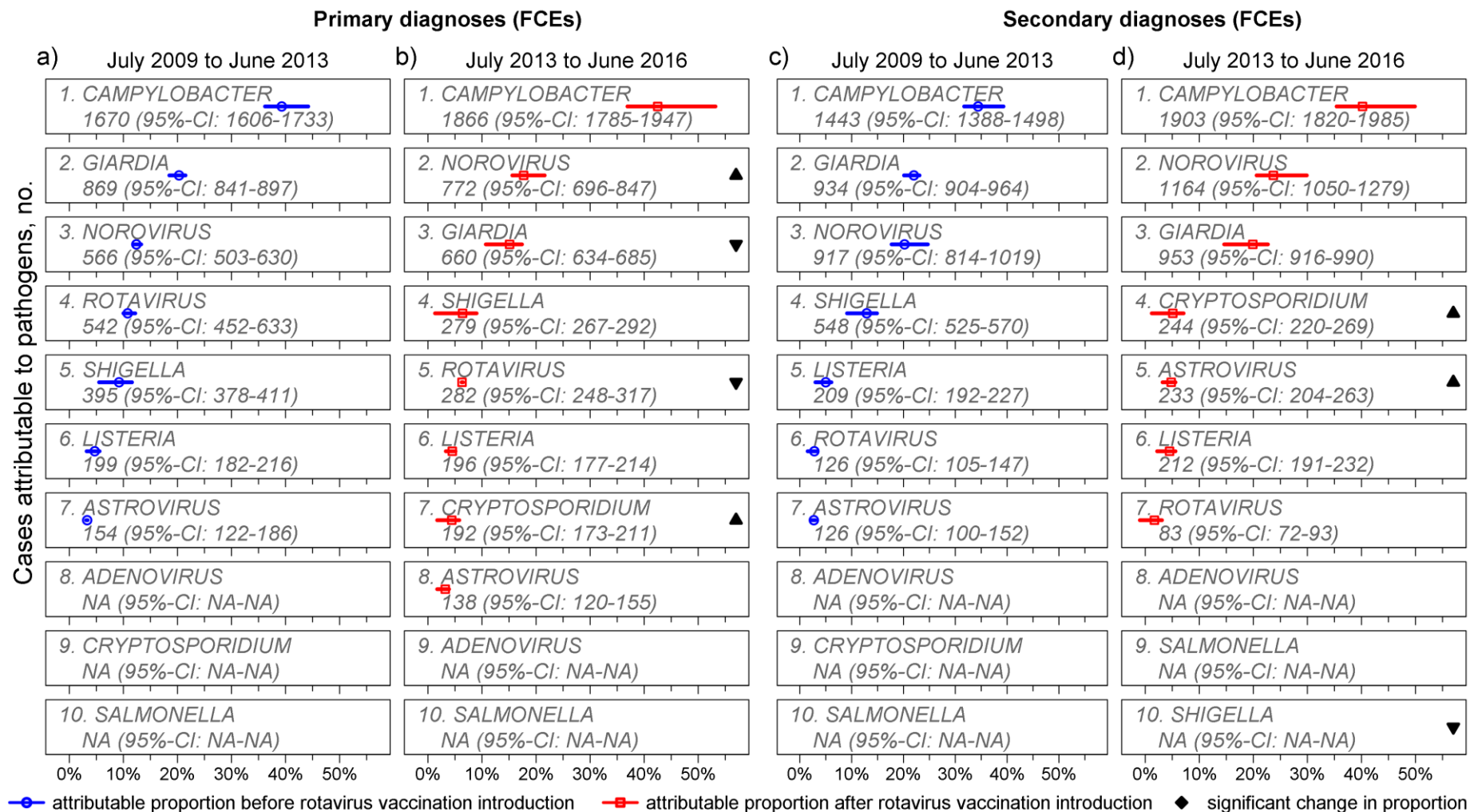
*' in this table means a figure between 1 and 5, values suppressed to prevent possible identification of individuals.^[244]

4.5.2 Statistical analysis to estimate the burden of disease

4.5.2.1 Linear regression model results

The regression models with the highest goodness-of-fit showed a significantly increasing proportion of primary and all diagnoses being attributable to norovirus after July 2013, while the proportions of rotavirus-attributable primary and all diagnoses decreased significantly after July 2013 (Supplementary Table 22 and Figure 16). Due to the heterogeneity across the seven seasons, this study continues reporting results for July 2013 to June 2016. Moreover, the significant reduction in rotavirus diagnoses was driven by 0–4 year olds, while the significant increase for norovirus was driven by patients aged 0–64 year olds (Supplementary Figure 19). Given that confidence intervals for norovirus overlapped across age groups, this study continues reporting non-stratified results.

Figure 16. Attributable fraction (in %) of enteric pathogens on all-cause acute gastrointestinal primary and secondary diagnoses in hospitals in England, using linear regressions fitted to the data of July 2009 to June 2013 vs. July 2013 to June 2016. Estimated absolute numbers provided for information.



Between July 2013 and June 2016, the best-fitting regression models attributed 17.7% of primary gastrointestinal diagnoses (95%-CI: 15.6%–21.6%) and 23.8% (95%-CI: 20.6%–29.9%) of secondary gastrointestinal diagnoses to norovirus (Figure 15), leading to a median estimate of 40,800 (IQR: 40,500–41,400) norovirus-associated cases with primary and 61,500 (IQR: 58,700–62,500) with secondary diagnoses annually. Results were slightly lower when limiting the data to December 2015 to include STEC (Supplementary Table 23).

4.5.2.2 Multi-state model results

The mean excess length of hospital stay due to norovirus was estimated at 3.3 days (95% CI: 0.2–6.5). Patients with norovirus infection and a secondary gastrointestinal diagnosis stayed an excess 4.0 days (95% CI: 0.4–7.6).

4.5.2.3 Bed-days kept unoccupied for infection control

A median 19.7%–26.3% of bed-days lost in outbreaks voluntarily reported to HNORS by acute care hospitals during the winters of 2013/14 to 2015/16 matched with those mandatorily recorded by NHS England (Supplementary Table 26).

4.5.2.4 Total number of bed-days used for norovirus

Annually, at least 290,000 (IQR: 282,000–297,000) occupied and unoccupied bed-days were norovirus-attributable using conservative estimates (Supplementary Table 29), with 28% being used by inpatients with a primary diagnosis, 62% by secondary diagnoses, and 10% were beds that had been closed unoccupied.

4.5.2.5 Staff absences due to norovirus

An estimated median 4,200 (IQR: 3,800–5,100) members of staff were absent during norovirus outbreaks annually between mid-2013 and mid-2016.

4.5.3 Costing the burden of disease

4.5.3.1 Direct expenditures incurred due to norovirus

Norovirus-associated gastroenteritis incurred direct expenditures of £107.6 million (IQR: £104.6–£109.8 million) annually, of which £8.9 million (£8.6–£10.4 million) were lost on unoccupied bed-days. Staff absences due to infection incurred costs for the NHS of £1.3 million (£1.2–£1.6 million) annually. The 15% variable costs proportion indicates potential monetary savings from averting all norovirus cases equivalent to £16.1 million (£15.7–£16.5 million).

4.5.3.2 Opportunity costing

The 290,000 norovirus-associated bed-days could have been used for 57,800 (56,400–59,200) alternative non-gastroenteritis patients, who would have been expected to gain 13,800 (13,500–14,100) QALYs at a net monetary benefit of £190.1 million (£185.5–£194.7 million). From a health-maximising perspective, the forgone non-gastroenteritis patients were expected to have gained a higher net benefit than the norovirus cases (Supplementary Table 31), with the value of the opportunity costs approximating to £297.7 million (£290.1–£304.5 million) and losing an estimated 6,300 QALYs (i.e. 13,800 minus 7,500; cf. Supplementary Material 4.10.8).

4.5.3.3 Sensitivity analysis

Sensitivity analyses confirmed that the wide uncertainty range around the excess length of stay estimate was the most influential source of uncertainty for the burden estimation (Supplementary Material 4.10.9).

For the estimation of the costs, the monetary value assigned to QALYs was the most influential parameter with a direct impact on the estimates of the opportunity costs and economic costs (Supplementary Material 4.10.9).

4.6 DISCUSSION

This study quantified the hospital burden of norovirus-associated gastroenteritis for the NHS in England. In addition to the clinical harm to patients from gastroenteritis, this

study included for the first time the wider health impact that infectious diseases like norovirus can have for other patients awaiting admission by reducing the beds and staff available to them.^[260]

4.6.1 Summary of key findings and clinical implications

Of all inpatients with primary or secondary all-cause gastrointestinal diagnoses in England between July 2013 and June 2016, 18% (95%-CI: 16%–22%) and 24% (95%-CI: 21%–30%) were attributable to norovirus, respectively. While the general increase in patients diagnosed with gastrointestinal illnesses in England throughout this period seemed to be driven by secondary diagnoses, the increase in norovirus-attributable inpatients identified after July 2013 appeared to be driven by primary diagnoses (less so by secondary diagnoses or outbreaks, cf. Supplementary Table 20; or coding variations, cf. Supplementary Table 19). Gastrointestinal inpatients have been discharged faster in recent years (Supplementary Material 4.10.1), in line with the generally decreasing length of hospital stays in the past decade,^[244] presumably giving norovirus less time to spread. Moreover, enhanced hygiene and other infection control measures^[87,107,108] as well as a potentially increasing awareness^[107] may have contributed to fewer secondary norovirus-associated hospital cases and norovirus outbreaks.

The regression results also showed that norovirus is now the second-highest contributor of gastrointestinal hospital diagnoses, after *Campylobacter*. The proportional increase in the burden of norovirus is largely driven by the reduction in rotavirus, which led to a reduced total number of laboratory-confirmed cases (cf. Supplementary Table 20). Overall, the total number of bed-days tied up by norovirus-associated gastroenteritis annually is equivalent to the entire daily NHS hospital bed capacity in England being unavailable for more than two days (i.e., 290,000/133,000).^[7] The bed-days lost to norovirus prevented admission of other patients, who are estimated to have the potential to gain twice as many QALYs from hospitalisation as the norovirus patients who displaced them. Therefore, these findings demonstrate the wider impact of norovirus outbreaks on health. In addition, a combined £10.3 million was lost annually from bed-days kept unoccupied and staff absences. For norovirus, with the prospect of several treatments and vaccines becoming available soon,^[56,95] these estimates may serve as baseline for their potential to reduce the hospital burden and free up beds and staff for new admissions.

4.6.2 Comparison with previous work

The estimate of 16% (95% CI: 15%–19%) of gastrointestinal patients attributable to norovirus for July 2009 to June 2013 in this study is consistent with a previous estimate of 17% (95% CI: 15%–19%) from a systematic review of studies published up to 2014,^[49] irrespective of novel norovirus strain emergences. After July 2013, this study estimated this increases to 21% (95% CI: 19%–25%), which is not attributable to the emergence of a novel norovirus strain, but appeared to be driven by statistically significantly higher proportions in children aged 0–4, 5–18 and adults aged 19–64 (Figure 16).

Previously, the costs attributable to unavailable bed-days due to norovirus-like symptoms for acute care hospitals were estimated as £35–£49 million in England each winter using the excess bed-day cost value for 2015/16.^[268] Another study estimated the hospital costs of gastroenteritis outbreaks in England at £115 million annually using a top-down approach and data from 1994/95 and 2002/03,^[41] which translates to costs from norovirus outbreaks of £96.9 million in 2016 value^[269] when accounting for norovirus being present in only 63% of gastroenteritis outbreaks.^[41] While higher expenditures of £107.6 million were estimated here, the economic costs of £297.7 million (including hospitalisations forgone) are almost thrice as large, reflecting greater accuracy by using individual-patient data, accounting for time-dependent biases,^[270-272] including non-acute care hospitals and maternity and mental health wards, and considering the opportunity costs for alternative patients forgone.

4.6.3 Strengths and limitations

This study is the first to combine individual-level norovirus outbreak data with national hospital surveillance and statistics to apply a novel method for estimating the opportunity costs of norovirus-associated gastroenteritis from patients who cannot be admitted due to beds being unavailable. This novel methodology of estimating opportunity costs is generalisable to other settings given that occupancy rates of hospital beds are high in other places besides England.^[6,7] Moreover, given the interest in the economic value of the bed-days that could not be used for alternative admissions, no actual cases may have always been delayed or cancelled. Furthermore, the approach could be applied to other (infectious) diseases, and to community settings using e.g. general practitioner visits

instead of hospitalisations.^[260] The potential for these analytical approaches is likely to increase in future given the increasing number of linkable data sources.

The study here used the best available data sources for norovirus, which were adjusted for bias in reporting.^[52,259] Unadjusted HNORS data were not used directly due to under-reporting of outbreaks, cases and bed-days. Although the regression analysis assumed independence of observations, it is a well-described method to quantify the aetiology of gastroenteritis^[115,116,273] that captures correlations in weekly counts implicitly through the explanatory variables. Given the large sizes of the data used for the regression analysis a linear model was chosen, however results are also robust to a negative binomial model (Supplementary Material 4.10.2). The regression also accounted for potential miscoding of intestinal diagnoses,^[115,116] and a statistically rigorous method was used to estimate the excess length of stay.^[270-272] A possible limitation is the use of the local data to model length of stay and the expected QALY gain from hospital treatment. Moreover, the previously estimated 20% under-reporting of outbreaks was taken as a conservative estimate; the actual number of outbreaks may be higher. Likewise, the actual number of bed-days lost unoccupied remains uncertain due to the voluntary reporting to HNORS, and is likely higher than conservatively assumed here despite the efforts of matching the bed-days. Future research should consider larger norovirus samples through advanced individual-patient infection control during outbreaks and longer observation periods. Moreover, clinical hospital diagnoses may not fully capture patients with asymptomatic carriage of norovirus.^[274] Nonetheless, this study is first to estimate the expected QALY gain from hospital treatment in England, and the results for the sample of non-gastroenteritis patients can readily be used in other studies.

The need to differentiate inpatients by their primary and secondary norovirus diagnosis arose mainly in order to not bias the total number of bed-days used for norovirus systematically upwards.^[270-272] Therefore, this study relied on records of intestinal illness episodes in hospital; if illnesses are incompletely recorded the burden estimate of this study may be an underestimate. Also, secondary diagnosis codes may be less reliable due to potential variation in coding practices between hospitals.^[244] Note that a secondary diagnosis does not necessarily imply a hospital-acquired infection. From the economic perspective of this study, however, the source of infection, i.e. hospital-acquired or community-acquired, is irrelevant for obtaining a comprehensive picture of the burden of norovirus in hospitalised patients.

While the local sample did not involve paediatric or elderly wards, these were included in the national sources. Future research may need to investigate norovirus transmission rates for different age groups. When stratifying regressions by age, confidence intervals overlapped, which supports a previous systematic review and meta-analysis that found similar norovirus attributable fractions among all-cause gastroenteritis for patients below the age of 5, 5 years and older, and mixed ages.^[49]

For the bed-days kept unoccupied, the figures reported to HNORS and NHS England were matched as closely as possible for a fair comparison, and it was assumed that the observed difference applied throughout the year and equally to community hospitals and maternity and mental health wards.

The staff absence costs in this study are likely to be still an underestimate due to considering only outbreaks and the average wage of nurses but no other healthcare professionals nor relief/locum staff. Other studies of norovirus outbreaks in England and Scotland applied the same assumptions, with their proportions of staff absence costs on the total expenditure reaching 0.25^[41] and 0.17^[258], while the estimated staff costs made up about 0.03 here. This study also did not consider indirect costs from productivity losses nor the costs borne by the community (or in long-term care facilities), which would substantially increase costs.^[55,254,275]

The results support the hypothesis that a norovirus vaccine may have the greatest impact in reducing the burden of norovirus-associated gastroenteritis cases and outbreaks in hospital settings when reaching adult and the elderly populations, particularly those at risk of secondary infection while staying in hospital (Figure 16 and Supplementary Figure 17). However, future research needs to investigate the potential impact of vaccinations and treatments on disease dynamics, and the most appropriate target groups to prevent transmission, such as adult inpatients, staff and children.^[79]

4.7 CONCLUSION

With bed pressures being a recurring public health concern, any analysis considering the impact of infectious diseases on hospital systems needs to include the opportunity costs from forgone alternative admissions. In England, although the hospital burden of rotavirus has declined significantly following vaccination introduction in July 2013, the overall number of gastrointestinal inpatients has kept growing with a significantly

increasing proportion of primary diagnoses being attributable to norovirus. In fact, norovirus has become the second largest contributor of inpatient gastrointestinal illnesses in England since mid-2013. Norovirus-associated gastroenteritis ties up the equivalent of more than twice the daily hospital bed stock in England, with a substantial economic and health impact for the NHS and patients.

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Listeria and shiga toxin-producing *E. coli* (STEC) from the National Enhanced Surveillance System for STEC (NESSS) and from national surveillance of listeriosis in England and Wales. Hospital Episode Statistics (HES) of the Health and Social Care Information Centre, Copyright © 2017, were re-used with the permission of the Health and Social Care Information Centre. All rights reserved.

4.10 SUPPLEMENTARY MATERIAL

4.10.1 Additional information on data sources

The hospital burden of norovirus-associated gastroenteritis was estimated based on a) patients, b) the bed-days occupied by these patients, c) bed-days kept unoccupied for infection control, and d) staff absences due to infection. While the starting point of this analysis was the national hospital surveillance system of norovirus outbreaks, HNORS, this system only tracks outbreaks and relies on voluntary reporting. As such, HES data were used to obtain all norovirus-attributable gastroenteritis patients, and the voluntarily reported numbers of lost bed-days and staff absences in HNORS were used as basis for the estimation after adjusting for potential under-reporting.

4.10.1.1 Number of patients, bed-days lost, and staff absences during norovirus outbreaks

The Hospital Norovirus Outbreak Reporting System (HNORS) gathers voluntarily reported information of norovirus outbreaks since its inception in January 2009. In total, HNORS included 8,767 outbreaks at the time of data retrieval (August 2016). Incomplete outbreaks up to June 2009 were excluded as they counted towards various previous epidemiological seasons (n=609), and outbreaks for the season of 2016/17 (n=16). In total, 8,142 outbreaks in 439 hospitals and 147 Trusts across the seven seasons from July 2009 to June 2016 were considered in the analysis. Most outbreaks involved general medicine wards (n=1,754; 21.5%), followed by elderly care wards (n=1,587; 19.5%) and acute medicine (n=511; 6.3%). Paediatric wards were only involved in a small number of outbreaks (n=88; 1.1%).

4.10.1.2 Hospital statistics for gastrointestinal illnesses

The Hospital Episode Statistics (HES) database holds inpatient records including one primary and up to 19 secondary diagnoses that are recorded at the time of discharge.^[244] Gastrointestinal infectious and non-infectious illnesses (ICD10 codes A00–A09; K528 and K529) were extracted per date of admission for finished consultant episodes using only primary diagnosis codes, only secondary diagnosis codes, or all diagnosis codes of all ordinary admissions, day cases, and mothers and babies using only delivery facilities. It was ensured that patients with secondary diagnoses were not double counted given that records can have more than one gastrointestinal diagnosis code, and also both a primary plus secondary diagnosis code (which were counted as primary diagnosis).

Given that the HES data are recorded per financial year (i.e., from April in the first year up to the end of March of the following year), records for 2016/17 were obtained too in order to obtain data up to week 26 in 2016 to derive the entire epidemiological season for 2015/16.

Interestingly, a change in coding practices led to an increase in infectious intestinal diagnoses on all gastrointestinal diagnoses from 22.9% to 87.1% starting in financial year 2012/13 (Supplementary Table 19). As such, infectious and non-infectious gastrointestinal diagnoses were combined in the analysis in order to minimise the impact of coding variations over time.

Table 19. Coding of infectious and non-infectious intestinal diagnoses in England over time, 2009/10–2015/16.

Season	2009/ 2010	2010/ 2011	2011/ 2012	2012/ 2013	2013/ 2014	2014/ 2015	2015/ 2016	2009/10– 2011/12	2012/13– 2015/16
Patients with primary gastrointestinal diagnoses									
infectious ^a	0.312	0.300	0.288	0.859	0.869	0.863	0.857	0.300	0.861
non-infectious ^b	0.688	0.700	0.712	0.141	0.131	0.137	0.143	0.700	0.139
Patients with secondary gastrointestinal diagnoses									
infectious ^a	0.181	0.159	0.153	0.871	0.890	0.887	0.883	0.159	0.883
non-infectious ^b	0.819	0.841	0.847	0.129	0.110	0.113	0.117	0.841	0.117
Patients with primary or secondary gastrointestinal diagnoses									
infectious ^a	0.248	0.229	0.221	0.865	0.880	0.876	0.871	0.229	0.871
non-infectious ^b	0.752	0.771	0.779	0.135	0.120	0.124	0.129	0.771	0.129

Note: Data represent financial years.

a: ICD-10 codes A00–A09 across all ages.

b: ICD-10 codes K528 and K529 across all ages.

4.10.1.3 Hospital statistics for gastrointestinal illnesses: Further dynamics observed

Patients with a primary gastrointestinal diagnosis have used statistically significant fewer bed-days over the years, with a median 2.21 (IQR: 2.21–2.24) bed-days before mid-2013 and 1.99 (IQR: 1.96–1.99) afterwards (Supplementary Table 20).

Moreover, the increase of primary gastrointestinal diagnoses appeared to have been halted for most age groups after introducing the rotavirus vaccine (Supplementary Figure 17); the further increase for adolescents seemed minor given the low number of cases. More importantly, the very high peaks for young children (aged <5 years) disappeared after July 2013, which included the primary target group of the rotavirus vaccination campaign.^[276] Unlike primary diagnoses, the number of inpatients with secondary gastrointestinal diagnoses continued to increase across all ages except for young children (aged < 5 years), whose peaks also flattened slightly (Supplementary Figure 17). However, winter peaks were still visible for young children (aged <5 years) and the elderly.

Consequently, in health care settings the major gastrointestinal disease burden now rests with adults and the elderly since July 2013, particularly for patients with secondary gastrointestinal diagnoses (cf. Supplementary Table 20 and Supplementary Figure 17; note the different scales in Supplementary Figure 17).

Table 20. Raw input data of the national data sources in England per season, for NHS England per winter.

Source	Variable	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
SGSS/NESSS /national surveillance of listeriosis ^a	Adenovirus (group F serotype 40 & 41)	169	181	198	152	135	45	47
	Astrovirus	66	49	78	397	291	284	304
	<i>Campylobacter</i>	57,926	59,262	60,943	57,046	58,156	55,643	50,348
	Cryptosporidium	4,471	3,490	3,199	5,331	3,129	3,579	5,354
	STEC (shiga toxin- producing <i>E. coli</i>)	933	1,003	871	725	784	780	430 ^f
	Giardia	3,398	3,676	3,640	3,594	3,513	3,972	4,398
	Listeria	179	167	159	178	182	162	188
	Norovirus	12,216	7,784	8,669	9,459	4,761	7,635	6,313
	Rotavirus	15,245	14,894	14,935	14,686	4,429	4,430	2,345
	Salmonella (excl. typhi & paratyphi)	8,824	8,306	7,300	7,088	6,538	7,888	7,946
	Shigella	1,554	1,932	1,727	1,935	2,029	2,184	1,848
	Total		104,981	100,744	101,719	100,591	83,947	86,602
HES ^b	Primary diagnoses	227,000	220,200	233,100	247,400	226,300	236,600	230,800
	Primary diagnosis (bed-days)	568,400	507,400	495,100	507,500	459,900	471,500	434,100
	Secondary diagnoses	220,900	219,300	228,700	243,100	234,900	258,500	267,000
	~ of which day cases	24,300	26,900	30,600	30,800	31,500	35,400	39,100
	All diagnoses	448,000	439,500	461,800	490,400	461,200	495,100	497,800
HNORS ^c	Outbreaks	1,900	1,200	1,600	1,500	600	900	500
	Patients	19,500	11,500	15,500	14,000	5,400	7,700	4,300
	staff absences	5,200	3,000	3,700	3,500	1,400	2,100	1,300
	lost bed-days	22,900	15,300	17,200	16,900	7,400	12,400	7,200
NHSE ^d	unoccupied bed- days	n/a ^e	24,100- 31,700	32,100- 42,600	32,600- 41,900	19,800- 25,500	24,800- 32,700	8,700- 11,500

Abbreviations: HES: hospital episode statistics, HNORS: Hospital Norovirus Outbreak Reporting System, NESSS: National Enhanced Surveillance System for STEC, NHSE: National Health Service England, SGSS: Second Generation Surveillance System, STEC: shiga toxin-producing *E. coli*.

a: Note that the aggregate figures do not account for seasonality within each year.

b: Figures of finished consultant episodes were extracted for financial years but are shown here per season, i.e. week 27 in the first year to week 26 in the following year.

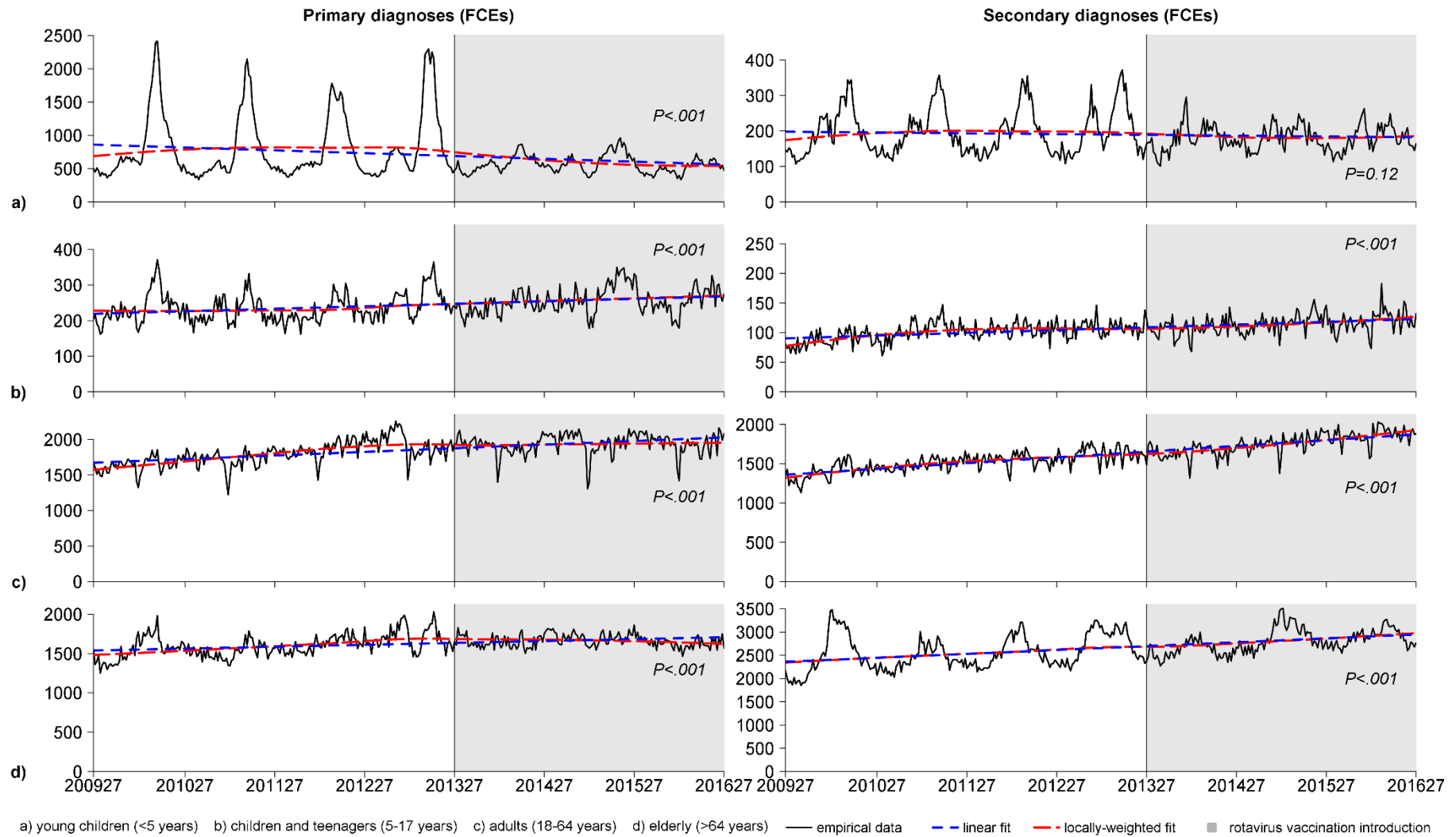
c: Recording started in week 1 in 2009; values presented here represent seasons running from week 27 in the first year to week 26 in the second year; thus e.g. the first season 2009/10 covered the period of week 27 in 2009 to week 26 in 2010.^[71]

d: Missing values on weekends and public holidays were imputed in best-to-worst-case scenarios; values presented here were recorded between November and March for 16, 18, 17, 21, 21, and 13 weeks for the six seasons, respectively; for a sound comparison see ^[268].

e: The first winter recorded by NHS England was in 2010/11.

f: For season 2015/16, no reports for shiga toxin-producing *E. coli* (STEC) were available for the year 2016 due to the data being audited.

Figure 17. Additive decomposition of national hospital statistics into age-stratified inpatients with primary and secondary gastrointestinal diagnoses in England, July 2009 to June 2016 (cave: different scale of y-axes).



4.10.1.4 Laboratory data of gastrointestinal pathogens

The weekly number of de-duplicated laboratory reports were obtained using the date of the first specimen from faeces and lower gastrointestinal tract from reports submitted by microbiology laboratories across England to Public Health England. While reporting to Public Health England is mandatory for some enteric pathogens like *Salmonella*, it is voluntary for e.g. norovirus and rotavirus; however, laboratory testing and reporting practices have been confirmed to be high and consistent in a survey for rotavirus before.^[277]

For rotavirus, laboratory reports showed a decrease after July 2013 when the vaccine was introduced,^[276] while for norovirus they remained relatively constant with peaks in 2009/10 and 2012/13 that corresponded to novel strain emergences^[58] (Supplementary Table 20). At the same time, the total number of laboratory reports decreased after July 2013 from a median 101,200 (IQR: 100,700–102,500) reports before mid-2013 to 83,900 (IQR: 81,700–85,300) afterwards (Supplementary Table 20). Note: The aggregate figures of pathogens do not account for seasonality within the years, which is why the regression models based on the weekly data provide more accurate results than a comparison of the raw data.

4.10.1.5 Patient-level data of norovirus infections from a local hospital

This study used individual-level patient data collected in a teaching hospital in London during a norovirus outbreak in 2015, during which the lower daily admission than discharge rates (of 0.208 vs. 0.212, respectively) corresponded to the outbreak potentially having prevented new admissions. At the time of the outbreak, the four wards had a capacity of 56, 59, 56 and 43 beds, which is larger than the median 20 beds (range 1–38) reported previously for 171 units in another region in England in 2002–2003;^[41] however, the wards included one admission ward, one general ward and two infectious disease wards with isolation bed capacity. As such, it was assumed that the setting was negligible for estimating the excess length of stay of patients with norovirus (it may rather have had a positive effect on the speed of containing the outbreak).

For the analysis of the routinely collected patient data, this study copied for duplicate records of the same patients any missing personal information (i.e., date of birth and sex) and any missing information of the same stay when a transfer occurred merely between

specialties, which led to another record being created (i.e., admission and discharge). For all records, missing information on the length of hospital stay were approximated with the stay on the wards.

Duplicate records of the same stay but not for different stays were removed. By using the first positive norovirus GII infection sample during the hospital stay it was ensured norovirus patients were not double counted as records of re-admissions were excluded when no other norovirus GII infection sample was taken. For stays beyond the observation period, the infection status was unknown and records censored to these time points.

In order to obtain unbiased controls without gastroenteritis, patients were excluded from the analysis that had a) any secondary infectious or non-infectious intestinal disease codes (A00–A09; K528 and K529), b) a primary non-infectious intestinal disease code (K528 and K529) or c) a negative PCR test taken for norovirus GII due to potentially being infected with a different norovirus strain, or a different enteric pathogen (e.g. 43.5% of cases during the local outbreak in 2015 were symptomatic yet tested norovirus GII negative, while 17.4% of cases were positively tested but asymptotically infected). For the demographic characteristics of all patients, together with those excluded, see Supplementary Table 21.

Table 21. Demographic characteristics of the local sample of patients from a teaching hospital in London, England, on the wards affected by the norovirus outbreak of May 31 to June 15, 2015, and the previous two years.

Variables	All patients	Excluded patients	All patients analysed	All controls	All cases
Patients, n (%)	2,855 (100.0%)	346 (12.0%)	2,509 (88.0%)	2,465 (86.3%)	44 (1.5%)
Age (years), mean (SD)	60.1 (20.4)	66.5 (21.0)	59.2 (20.2)	59.1 (20.1)	67.1 (20.9)
Sex (female), n (%)	1,456 (51.0%)	191 (55.2%)	1,265 (50.4%)	1,237 (50.2%)	28 (63.6%)
CCI score (>0), n (%)	1,667 (58.4%)	227 (65.6%)	1,440 (57.4%)	1,408 (57.1%)	32 (72.7%)
In-hospital mortality, n (%)	77 (2.7%)	23 (6.6%)	54 (2.2%)	*	*
LOS (days), mean (range)	6.3 (0, 43)	15.4 (0, 43)	5.0 (0, 43)	4.9 (0, 43)	12.6 (0, 43)
Excess LOS (days), mean (95% CI) ^a	n/a	n/a	n/a	n/a	n/a
QALY gain (undiscounted), mean (95% CI) ^b	0.183 (0.0001, 0.386)	0.220 (0.0002, 0.397)	0.179 (0.0001, 0.386)	0.178 (0.0001, 0.386)	0.193 (0.0004, 0.349)
QALY gain (discounted), mean (95% CI) ^b	0.147 (0.0001, 0.298)	0.182 (0.0002, 0.312)	0.142 (0.0001, 0.293)	0.142 (0.0001, 0.293)	0.160 (0.0004, 0.288)

CCI: Charlson comorbidity index, CI: confidence interval, GII: norovirus genogroup II, LOS: length of stay, n/a: not applicable, PCR: polymerase chain reaction, QALY: quality-adjusted life year, SD: standard deviation.

- a: No excess LOS is presented here given that hospitalisations for a primary infectious intestinal disease but without laboratory-confirmed norovirus diagnosis cannot necessarily be categorised as an excess stay.
- b: For cases, the QALYs gained were driven by the high level of comorbidities. If one approximates the gastroenteritis-related health gain by subtracting the QALY gain of all non-gastroenteritis control patients from the QALY gain of all gastroenteritis cases, one derives 0.160-0.142=0.018 QALYs gained.

‘*’ in this table means a figure between 1 and 5, values suppressed to prevent possible identification of individuals.^[244]

4.10.2 Details on the linear regression analysis

In order to attribute norovirus to inpatients with gastroenteritis, the expected number of gastroenteritis cases caused by different gastrointestinal pathogens per week was estimated using multiple linear regressions with laboratory reports for the pathogens as explanatory variables. The linear regression estimated the expected number of gastroenteritis inpatients Y using the gastrointestinal pathogens in week j :

$$Y_j = c + \sum \alpha_i L_{ij}$$

where L_{ij} denotes the number of laboratory reports for the gastrointestinal pathogens i in week j , α_i is the regression coefficient for pathogen i to estimate the number of inpatients with gastroenteritis diagnoses associated with each laboratory report, and c is a constant term for the background number of gastrointestinal illnesses that the model was not able to attribute to the weekly observations of laboratory reports. Similar to previous studies,^[115,116,273] the initial model included all pathogens, which were subsequently removed stepwise backwards when they were not significantly contributing to the model (i.e., $P < .05$ and their removal did not decrease the adjusted R^2), or that had a biologically implausible negative coefficient. The regression coefficient per pathogen were then multiplied with its observed number of laboratory reports before deriving the attributed fractions from the fitted total of hospital cases. Various sensitivity analyses were performed of excluding the constant, using only norovirus as explanatory variable, and separating the data to account for rotavirus vaccine introduction in July 2013. In a separate analysis, the data were limited up to December 2015 to be able to include shiga toxin-producing *E. coli* (STEC).

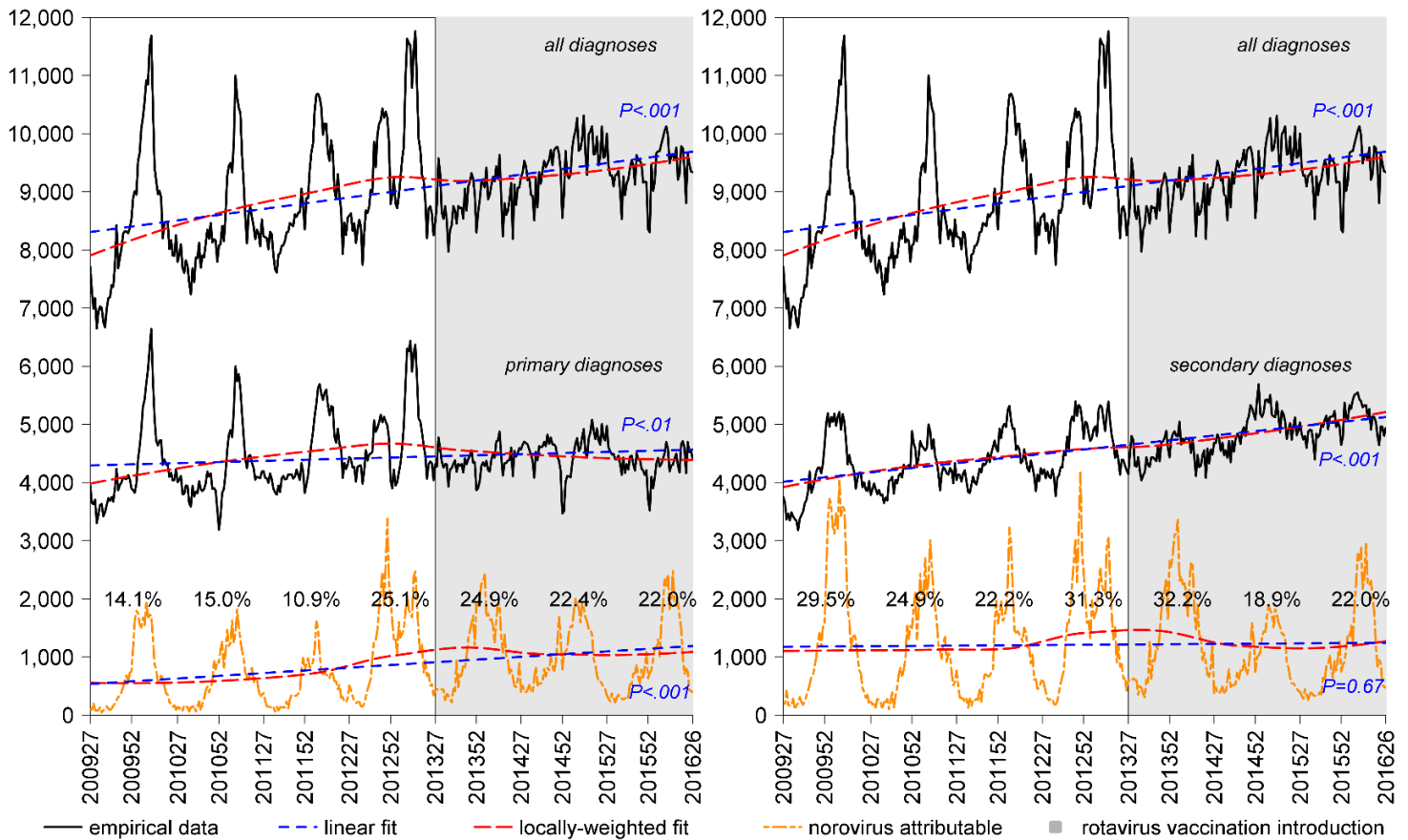
The regression models with the highest adjusted R^2 were those that separated the dataset in mid-2013 to account for rotavirus vaccination introduction, excluded the constant, and controlled for other significant pathogens besides norovirus, particularly astrovirus, *Campylobacter*, *Giardia*, *Listeria*, rotavirus and *Shigella* (Supplementary Table 22). The best-fitting models confirmed previous studies on rotavirus vaccination^[118,119] by showing a significant decrease in the burden attributable to rotavirus admissions following vaccine introduction in July 2013.

The results of the separate analysis that limited the data to December 2015 to include STEC showed slightly lower results for norovirus that were not significant when

separating the dataset in mid-2013 for rotavirus vaccination introduction (Supplementary Table 23). Because STEC was excluded in all but one regression model (and not the best-fitting one), where it accounted for only 1.6% (CI: 0.5%–2.4%) of primary diagnoses, the study proceeded without STEC in the interest of being able to use a longer dataset that captured the full seasonal activity of norovirus in 2015/16.^[71]

It was also checked how the regression models would predict the norovirus-attributable burden for each season and visualised results for the best-fitting models (Supplementary Figure 18). Despite a decreased power from fewer observations, proportions of above 20% were found for norovirus-attributable primary gastroenteritis for each season after mid-2013 (despite not including a novel strain emergence). The increase to about 25% already in 2012/13 corresponded with the Sydney/2012 norovirus strain emergence,^[58] while the consistently high levels afterwards corresponded with the rotavirus vaccination introduction.^[276] For secondary diagnoses, the fluctuations also correspond to the novel strain emergences in 2009/10 and 2012/13 (where values are at about 30%, while most other seasons are at lower levels of 20%) and the fewer reported norovirus outbreaks in HNORS in recent seasons. The strain emergence in 2012 was also much more efficient in transmission than the one in 2009, which may explain the lower fraction of primary diagnoses but higher fraction of secondary diagnoses in 2009/2010 (Supplementary Figure 18).

Figure 18. National hospital statistics for inpatients with infectious and non-infectious gastrointestinal illnesses in England, July 2009 to June 2016, and visualising norovirus-associated gastroenteritis using linear regressions fitted to the data per season.



Of note, a previous regression analysis found no increase in the number of (voluntarily-reported) norovirus outbreaks when using positive norovirus laboratory cases as explanatory variable.^[278] Differences to the findings here may be explained by the fact that a wider range of enteric pathogens were included as explanatory variables and the obligatory hospital diagnosis codes recorded for each gastrointestinal hospitalisation episode nationally were used as response variable.

Table 22. Attributable cause of gastrointestinal diagnoses by regression model, 2009/2010 to 2015/2016

Data, timeframe, model		Aden.	Astr.	Camp.	Cryp.	Giar.	List.	Noro.	Rota.	Salm.	Shig.	Intercept	Adj. R2
Primary gastrointestinal diagnoses (FCEs)													
2009/2010	Base analysis	-	3.3 (3.3–3.3)	8.8 (7.0–10.1)	0.7 (-0.6–1.6)	5.3 (2.3–7.4)	-	2.5 (1.7–3.1)	6.0 (5.6–6.6)	-	4.0 (1.9–5.5)	69.3 (63.3–77.9)	0.761
-	No constant	-	5.5 (5.5–5.5)	35.8 (33.6–38.8)	-	23.8 (23.5–24.0)	4.8 (3.6–5.6)	11.7 (11.3–12.3)	6.5 (6.3–6.9)	-	11.9 (9.4–13.6)	-	0.989
2015/2016	Noro only	-	-	-	-	-	-	7.8 (6.8–8.8)	-	-	-	92.2 (91.2–93.2)	0.295
2009/2010	Base analysis	-	2.6 (2.5–2.7)	12.7 (10.8–14.1)	2.3 (1.4–3.0)	-	-	3.7 (3.0–4.3)	9.4 (8.9–10.1)	-	1.7 (-0.9–3.7)	67.5 (63.3–73.1)	0.903
-	No constant	-	3.3 (3.1–3.4)	39.3 (36.2–44.2)	-	20.3 (18.5–21.5)	4.7 (3.2–5.6)	12.4 (11.8–13.3)	10.8 (10.0–12.2)	-	9.2 (5.5–11.6)	-	0.991
2012/2013	Noro only	-	-	-	-	-	-	11.1 (9.7–12.3)	-	-	-	88.9 (87.7–90.3)	0.393
2013/2014	Base analysis	-	-	12.8 (11.4–13.9)	-	5.7 (3.1–7.5)	-	5.8 (5.1–6.2)	4.3 (4.1–4.5)	3.6 (1.5–5.1)	-	67.8 (62.7–74.7)	0.578
-	No constant	-	3.2 (1.7–3.9)	42.5 (36.9–53.2)	4.4 (1.7–5.8)	15.1 (10.7–17.4)	4.5 (3.3–5.1)	17.7 (15.6–21.6)	6.3 (6.2–6.5)	-	6.4 (1.3–9.0)	-	0.993
2015/2016	Noro only	-	-	-	-	-	-	0.8 (-0.8–2.3)	-	-	-	99.2 (97.7–100.8)	0.000
Cases with secondary gastrointestinal diagnoses (FCEs)													
2009/2010	Base analysis	-	4.0 (3.7–4.3)	-	-	6.6 (3.4–9.3)	-	6.0 (5.5–6.4)	-	-	-	83.3 (80.0–87.4)	0.482
-	No constant	-	6.3 (6.2–6.4)	27.8 (27.0–29.1)	-	30.2 (29.6–31.1)	5.0 (3.4–6.1)	17.8 (16.1–20.5)	-	-	12.9 (9.5–15.1)	-	0.980
2015/2016	Noro only	-	-	-	-	-	-	6.7 (5.8–7.6)	-	-	-	93.3 (92.4–94.2)	0.273
2009/2010	Base analysis	-	2.3 (2.0–2.5)	-	-	-	-	8.6 (8.2–9.0)	0.7 (-0.1–1.3)	-	2.4 (-0.4–4.8)	86.0 (82.4–90.3)	0.750

– 2012/ 2013	No constant Noro only	-	2.7 (2.3–3.0)	34.4 (31.8–39.4)	-	22.0 (20.0–23.0)	5.0 (3.0–6.0)	20.2 (17.7–24.7)	2.7 (1.5–3.4)	-	13.0 (9.2–15.0)	-	0.984
		-	-	-	-	-	-	10.3 (9.5–11.0)	-	-	-	89.7 (89.0–90.5)	0.641
2013/ 2014	Base analysis	-	0.8 (-0.5–1.8)	-	-	6.6 (3.4–9.1)	-	7.9 (7.1–8.5)	-	-	-	84.8 (80.6–90.0)	0.484
– 2015/ 2016	No constant Noro only	-	4.7 (3.2–5.5)	40.2 (35.4–49.9)	5.1 (1.2–7.1)	20.0 (14.6–22.7)	4.5 (2.2–5.6)	23.8 (20.6–29.9)	1.8 (-0.9–3.1)	-	-	-	0.988
		-	-	-	-	-	-	7.7 (6.5–8.7)	-	-	-	92.3 (91.3–93.5)	0.442
All gastrointestinal diagnoses													
2009/ 2010	Base analysis	-	3.3 (3.1–3.5)	-	-	6.0 (3.4–8.0)	-	4.0 (3.4–4.5)	2.8 (2.6–3.0)	-	3.2 (0.9–5.0)	80.7 (76.0–86.6)	0.635
– 2015/ 2016	No constant Noro only	-	5.9 (5.8–6.0)	31.8 (30.1–34.3)	-	26.9 (26.7–27.4)	4.9 (3.6–5.8)	14.8 (13.9–16.2)	3.4 (3.0–3.6)	-	12.3 (9.6–14.2)	-	0.986
		-	-	-	-	-	-	7.3 (6.6–8.0)	-	-	-	92.7 (92.0–93.4)	0.388
2009/ 2010	Base analysis	-	2.5 (2.4–2.6)	5.0 (2.1–7.3)	-	-	-	5.8 (5.3–6.1)	5.1 (5.1–5.1)	-	2.7 (0.5–4.4)	78.9 (74.5–84.6)	0.868
– 2012/ 2013	No constant Noro only	-	3.0 (2.7–3.1)	36.8 (34.0–41.6)	-	21.1 (19.3–22.2)	4.8 (3.2–5.8)	16.2 (14.8–18.5)	7.0 (6.7–7.3)	-	11.0 (7.3–13.2)	-	0.989
		-	-	-	-	-	-	10.7 (9.8–11.5)	-	-	-	89.3 (88.5–90.2)	0.576
2013/ 2014	Base analysis	-	-	6.5 (4.0–8.4)	-	6.4 (4.4–8.0)	-	6.8 (6.3–7.2)	1.3 (0.6–1.8)	-	-	79.0 (74.6–84.8)	0.467
– 2015/ 2016	No constant Noro only	-	4.1 (2.6–4.9)	42.9 (38.1–51.5)	5.1 (2.0–6.8)	18.4 (13.6–21.2)	4.4 (2.6–5.4)	21.1 (18.9–25.0)	4.0 (2.7–4.7)	-	-	-	0.991
		-	-	-	-	-	-	4.4 (3.4–5.3)	-	-	-	95.6 (94.7–96.6)	0.299

Aden: Adenovirus, Astr: Astrovirus, Camp: Campylobacter, Cryp: Cryptosporidium, FCE: Finished Consultant Episode, Giar: Giardia, List: Listeria, NHS: National Health Service, Noro: Norovirus, Rota: Rotavirus, Salm: Salmonella (excl. typhi & paratyphi), Shig: Shigella.

The results of the most parsimonious models with the highest goodness-of-fit are presented in **bold**. 95% confidence intervals are given in parentheses.

Table 23. Attributable cause of gastrointestinal diagnoses by regression model, 2009/2010 to December 2015 in order to be able to include data on shiga toxin-producing *Escherichia coli* (STEC)

Data, time-frame, model	Aden.	Astr.	Camp.	Cryp.	Giar.	List.	Noro.	Rota.	Salm.	Shig.	STEC	Intercept	Adj. R ²
Primary gastrointestinal diagnoses (FCEs)													
2009/2010 Base analysis	-	3.1 (3.0–3.1)	9.7 (7.8–11.1)	-	6.1 (3.7–7.9)	-	2.3 (1.4–2.9)	6.6 (6.2–7.1)	-	5.0 (2.8–6.5)	-	67.2 (62.2–74.2)	0.774
- No constant	-	4.9 (4.9–5.0)	37.2 (34.8–40.6)	-	22.6 (21.9–23.0)	4.8 (3.5–5.6)	10.6 (10.3–10.9)	7.4 (7.1–7.9)	-	12.6 (10.2–14.2)	-	-	0.989
2015/2016 Noro only	-	-	-	-	-	-	8.0 (6.9–8.9)	-	-	-	-	92.0 (91.1–93.1)	0.307
2009/2010 Base analysis	-	2.6 (2.5–2.7)	12.7 (10.8–14.1)	-	-	-	3.7 (3.0–4.3)	9.4 (8.9–10.1)	-	1.7 (-0.9–3.7)	2.3 (1.4–3.0)	67.5 (63.3–73.1)	0.903
- No constant	-	3.3 (3.1–3.4)	39.3 (36.2–44.2)	-	20.3 (18.5–21.5)	4.7 (3.2–5.6)	12.4 (11.8–13.3)	10.8 (10.0–12.2)	-	9.2 (5.5–11.6)	-	-	0.991
2012/2013 Noro only	-	-	-	-	-	-	11.1 (9.7–12.3)	-	-	-	-	88.9 (87.7–90.3)	0.393
2013/2014 Base analysis	-	1.0 (-0.02–1.7)	13.2 (11.8–14.0)	1.6 (0.5–2.4)	6.4 (3.9–8.1)	-	5.1 (4.4–5.6)	5.1 (5.1–5.2)	3.7 (1.1–5.3)	-	-	63.9 (57.8–73.1)	0.625
- No constant	-	3.4 (2.1–4.0)	43.3 (37.2–55.3)	-	16.3 (12.4–18.3)	4.0 (2.4–4.9)	13.8 (12.7–16.2)	7.6 (7.2–8.4)	-	7.1 (1.6–10.0)	-	-	0.994
Dec 2015 Noro only	-	-	-	-	-	-	1.2 (-0.6–2.8)	-	-	-	-	98.8 (97.2–100.6)	0.005
Cases with secondary gastrointestinal diagnoses (FCEs)													
2009/2010 Base analysis	-	3.4 (3.2–3.6)	-	-	5.7 (2.3–8.4)	-	6.3 (6.0–6.5)	-	-	3.7 (0.6–6.1)	-	80.9 (75.4–87.9)	0.492
- No constant	-	5.3 (5.3–5.3)	29.7 (28.6–31.6)	-	28.2 (28.0–28.5)	4.7 (2.9–5.8)	17.5 (15.7–20.2)	-	-	14.6 (11.6–16.5)	-	-	0.981
2015/2016 Noro only	-	-	-	-	-	-	6.5 (5.6–7.4)	-	-	-	-	93.5 (92.6–94.4)	0.289
2009/2010 Base analysis	-	2.3 (2.0–2.5)	-	-	-	-	8.6 (8.2–9.0)	0.7 (-0.1–1.3)	-	2.4 (-0.4–4.8)	-	86.0 (82.4–90.3)	0.75

– No 2012/constant 2013 Noro only	-	2.7 (2.3–3.0)	34.4 (31.8–39.4)	-	22.0 (20.0–23.0)	5.0 (3.0–6.0)	20.2 (17.7–24.7)	2.7 (1.5–3.4)	-	13.0 (9.2–15.0)	-	0.984	
	-	-	-	-	-	-	10.3 (9.5–11.0)	-	-	-	-	89.7 (89.0–90.5)	0.641
2013/ Base 2014 analysis	-	-	-	-	8.6 (5.4–11.2)	-	7.8 (7.1–8.5)	-	-	-	-	83.6 (80.3–87.5)	0.465
– No constant Dec 2015 Noro only	-	4.4 (2.8–5.1)	41.2 (36.0–51.9)	5.7 (1.9–7.6)	21.9 (17.6–24.0)	3.3 (0.03–4.9)	20.3 (18.1–24.6)	3.2 (1.0–4.3)	-	-	-	-	0.989
	-	-	-	-	-	-	6.8 (5.6–8.0)	-	-	-	-	93.2 (92.0–94.4)	0.382

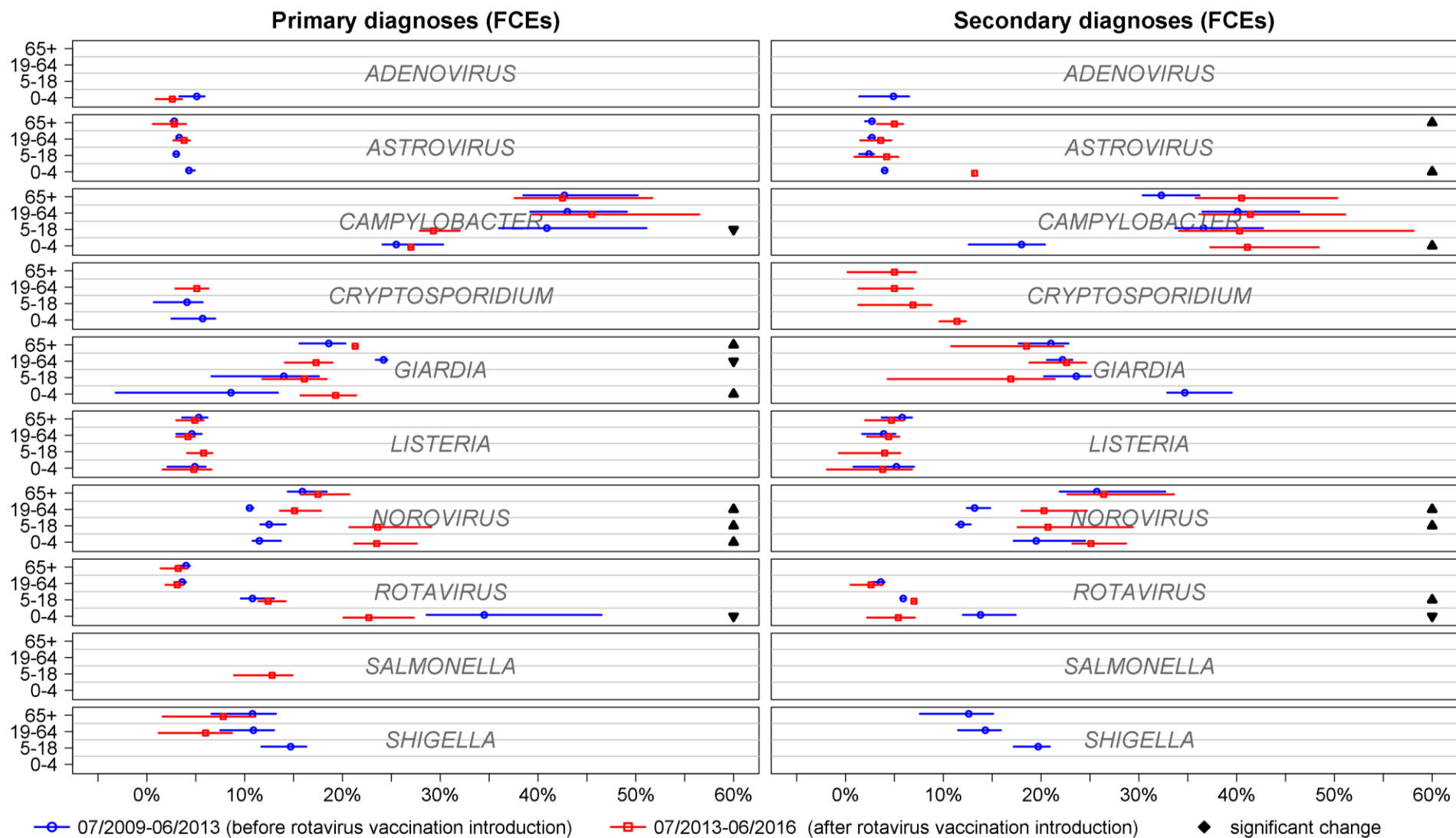
All gastrointestinal diagnoses

2009/ Base 2010 analysis	-	3 (2.7–3.1)	-	-	5.9 (3.2–8.0)	-	3.8 (3.1–4.3)	3.3 (3.1–3.4)	-	4.8 (2.5–6.5)	-	79.4 (74.7–85.3)	0.66
– No constant 2015/constant 2016 Noro only	-	5.2 (5.1–5.2)	33.3 (31.4–36.2)	-	25.4 (25.4–25.5)	4.7 (3.3–5.7)	13.6 (12.8–14.7)	4.2 (4.0–4.4)	-	13.6 (11.0–15.2)	-	-	0.987
	-	-	-	-	-	-	7.3 (6.5–8.0)	-	-	-	-	92.7 (92.0–93.5)	0.394
2009/ Base 2010 analysis	-	2.5 (2.4–2.6)	5 (2.1–7.3)	-	-	-	5.8 (5.3–6.1)	5.1 (5.1–5.1)	-	2.7 (0.5–4.4)	-	78.9 (74.5–84.6)	0.868
– No constant 2012/constant 2013 Noro only	-	3 (2.7–3.1)	36.8 (34.0–41.6)	-	21.1 (19.3–22.2)	4.8 (3.2–5.8)	16.2 (14.8–18.5)	7 (6.7–7.3)	-	11 (7.3–13.2)	-	-	0.989
	-	-	-	-	-	-	10.7 (9.8–11.5)	-	-	-	-	89.3 (88.5–90.2)	0.576
2013/ Base 2014 analysis	-	0.6 (-0.4–1.2)	9.4 (7.0–11.0)	1.3 (-0.3–2.5)	6.4 (3.3–8.6)	-	6.5 (6.1–6.8)	2 (1.4–2.5)	-	-	-	73.8 (67.5–82.8)	0.509
– No constant Dec 2015 Noro only	-	4 (2.6–4.8)	44 (38.8–53.4)	5.3 (2.1–7.0)	20.4 (16.4–22.6)	3.6 (1.2–4.9)	17.5 (16.1–20.0)	5.2 (4.4–5.7)	-	-	-	-	0.992
	-	-	-	-	-	-	4.1 (3.0–5.2)	-	-	-	-	95.9 (94.8–97.0)	0.255

Aden: Adenovirus, Astr: Astrovirus, Camp: Campylobacter, Cryp: Cryptosporidium, FCE: Finished Consultant Episode, Giar: Giardia, List: Listeria, NHS: National Health Service, Noro: Norovirus, Rota: Rotavirus, Salm: Salmonella (excl. typhi & paratyphi), Shig: Shigella, STEC: shiga toxin-producing *Escherichia coli*.

The results of the most parsimonious models with the highest goodness-of-fit are presented in **bold**. 95% confidence intervals are given in parentheses.

Figure 19. Age-stratified attributable fraction (in %) of enteric pathogens on all-cause acute gastrointestinal primary and secondary diagnoses in hospitals in England, using linear regressions fitted to the data of July 2009 to June 2013 vs. July 2013 to June 2016.



In Figure 19, the attributable fraction of enteric pathogens on gastrointestinal diagnoses were explored stratified by age. Pathogens are presented in alphabetical order given their different impact qua proportion in different age groups. Moreover, it needs to be kept in mind that this ecological regression analysis cannot inherently explain the reasons for the changes observed (e.g. in younger ages for norovirus), although it seems likely to be impacted by reductions in attributable cases for other pathogens, particularly rotavirus. Further in-depth analyses are required that were outside of the scope of this study.

Negative binomial regression models were also fitted to the data to compare with the multivariate linear regression models used in the paper. This allowed checking for over-dispersion by the rule of thumb of the residual deviance divided by the degrees of freedom being close to 1.0. This ratio was not higher than 1.05 in any of the models, indicating no over-dispersion.

For the norovirus-attributable burden, the values are indeed close to the multivariate regression although always slightly higher (see Table 24). The rest of the conclusions are not changing either.

The Akaike information criterion (AIC) of the models were then compared, with lower values indicating a (relatively) better fitting model. Overall, the linear regression models are almost always slightly better than the negative binomial models, except for the one of cases with secondary diagnoses before July 2013. Given the small difference though and the fact that the particular model was not used in the main results, the original estimates with the multivariate regression analysis were kept.

Table 24. Comparison of regression models; including results of norovirus-attributable proportions

Season	Linear regression	Negative binomial regression
Primary gastrointestinal diagnoses (FCEs)		
2009/10–2015/16	11.7 (11.3–12.3) AIC: 5553	14.6 (13.9–15.7) AIC: 5580 Dispersion: 1.02
2009/10–2012/13	12.4 (11.8–13.3) AIC: 3132	15.2 (14.0–17.1) AIC: 3141 Dispersion: 1.04
2013/14–2015/16	17.7 (15.6–21.6) AIC: 2312	19.3 (17.5–22.3) AIC: 2339 Dispersion: 1.05
Cases with secondary gastrointestinal diagnoses (FCEs)		
2009/10–2015/16	17.8 (16.1–20.5) AIC: 5784	20.0 (18.1–22.9) AIC: 5790 Dispersion: 1.02
2009/10–2012/13	20.2 (17.7–24.7) AIC: 3242	25.0 (21.6–31.0) AIC: 3236 Dispersion: 1.04
2013/14–2015/16	23.8 (20.6–29.9) AIC: 2432	26.1 (22.8–32.0) AIC: 2453 Dispersion: 1.04
All gastrointestinal diagnoses		
2009/10–2015/16	14.8 (13.9–16.2) AIC: 6164	18.1 (16.8–20.2) AIC: 6183 Dispersion: 1.02
2009/10–2012/13	16.2 (14.8–18.5) AIC: 3466	19.7 (17.5–23.3) AIC: 3470 Dispersion: 1.04
2013/14–2015/16	21.1 (18.9–25.0) AIC: 2583	22.6 (20.0–27.2) AIC: 2611 Dispersion: 1.05

AIC: Akaike information criterion, FCE: Finished Consultant Episode

4.10.3 Details on the multi-state model

The mean excess length of hospital stay due to norovirus was estimated using a multi-state model ^[270-272] consisting of four mutually exclusive states: admission, infected/diseased, discharged, and death (Supplementary Figure 20). Inpatients were allowed to make five transitions between two transient states for patients that do not, or do, develop norovirus, which are labelled in the following with “0” and “1”, respectively, and two absorbing states of being discharged alive or dead, respectively labelled with “2” and “3” (Supplementary Table 25 and Supplementary Figure 20). It was decided against a combined endpoint discharged/death given the rarity of in-hospital mortality among norovirus cases in the sample used, which conforms with national data;^[94] for most cases, the model thus estimated the excess length of stay based on control patients discharged alive (i.e., hazard rate λ_{12} vs. λ_{02} in Supplementary Figure 20).

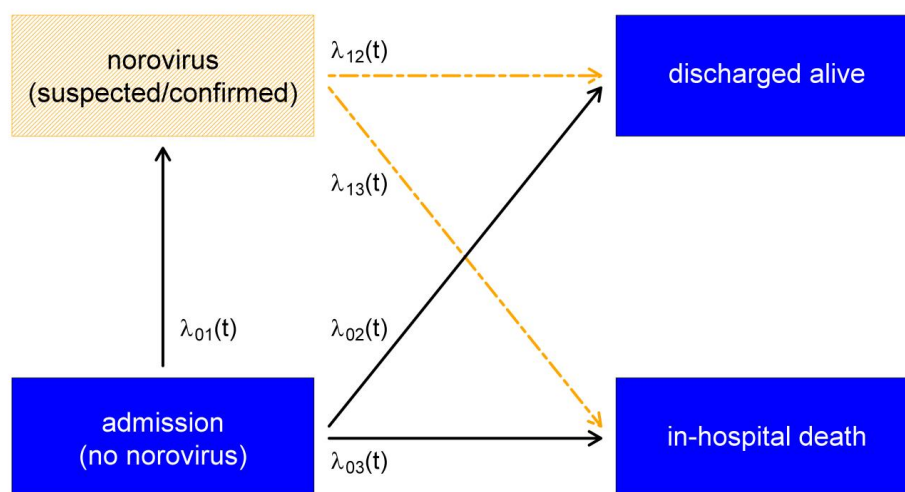


Figure 20. State-transition diagram of the multi-state model with hazard rates.

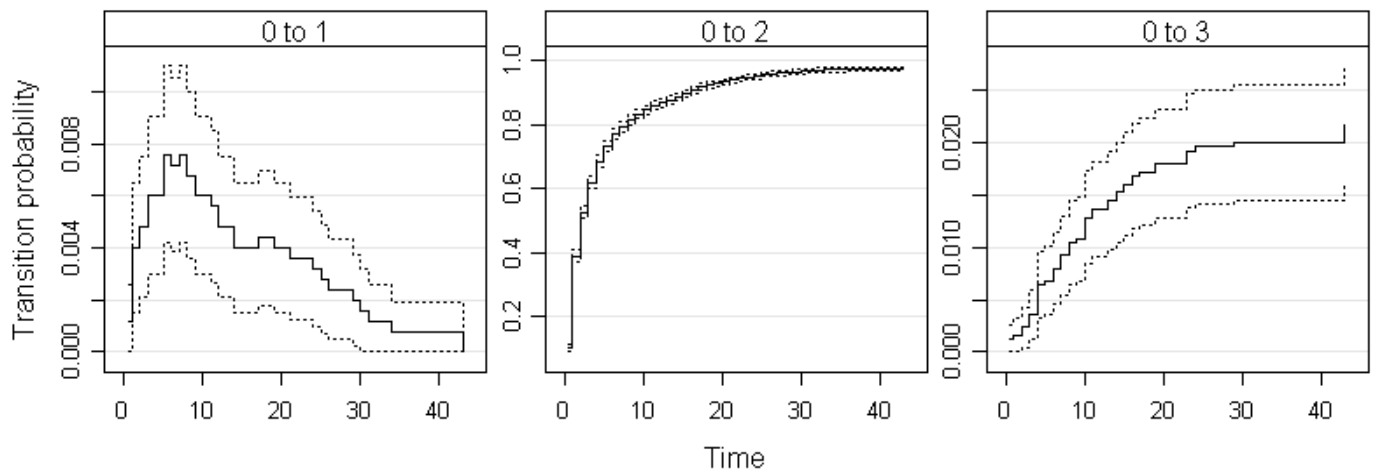
Table 25. Possible transitions of patients in the multi-state model

Transitions	from	to
Inpatients developing suspected and/or confirmed norovirus	0	1
Inpatients being discharged alive without developing norovirus	0	2
Inpatients dying in hospital without having developed norovirus	0	3
Inpatients being discharged alive after developing norovirus	1	2
Inpatients dying in hospital after having developed norovirus	1	3

The model was populated with the local patient-level hospital data that included the time of norovirus infection and symptoms. For day cases who did not stay overnight in hospital, the resource consumption was approximated with 0.5 bed-days. For primary gastrointestinal diagnoses, it was assumed that a diagnosis of primary gastrointestinal illnesses (as manifested by diarrhoea and/or vomiting) was made within about 15 minutes after being admitted (i.e., a value of 0.01).

The daily transition probabilities of patients were estimated as time-varying hazards using the empirical transition matrix (also called Aalen-Johansen estimator);^[263] cf. Supplementary Figure 21 for the 33 suspected and/or GII confirmed norovirus cases and 2,465 non-gastroenteritis controls.

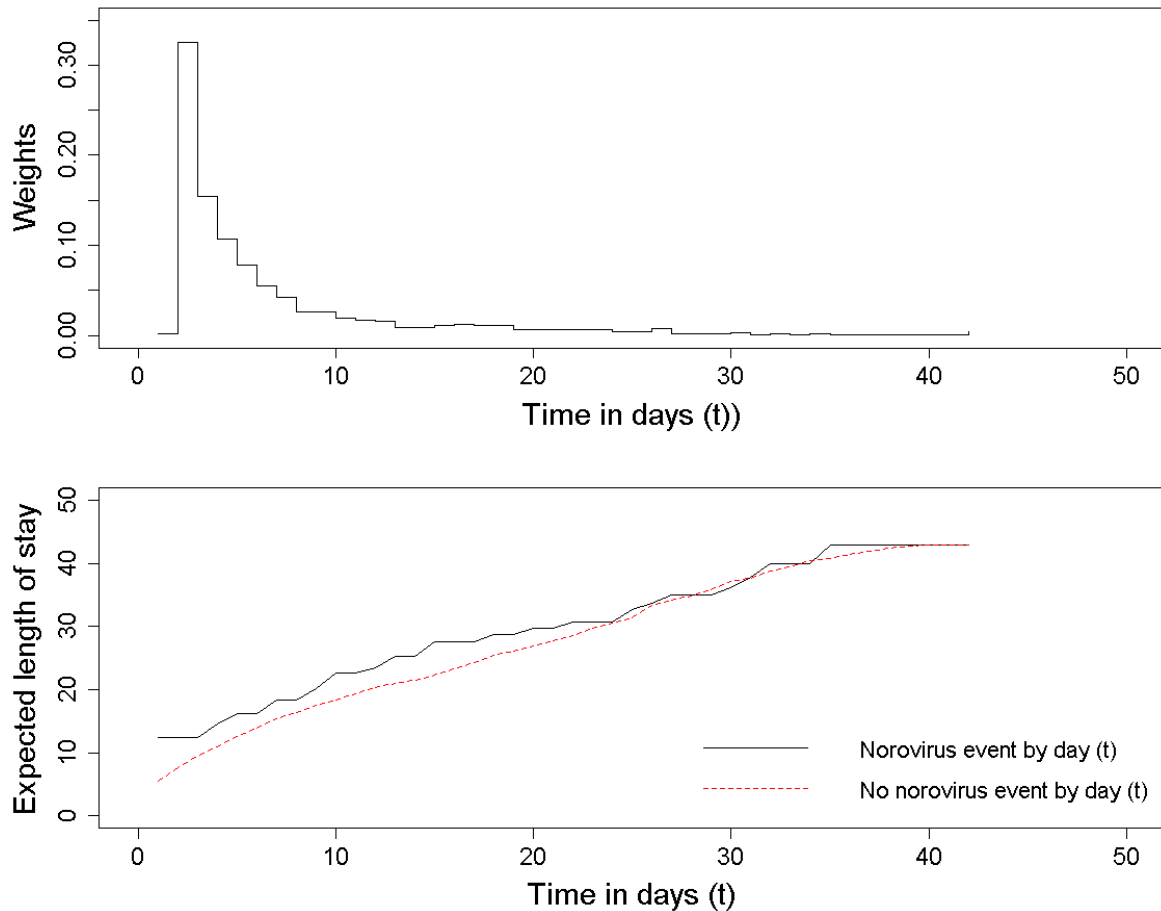
Figure 21. Transition probabilities from the individual-level patient data of developing norovirus (0 to 1), of being discharged alive without norovirus (0 to 2), of being discharged dead without norovirus (0 to 3).



Probabilities for norovirus not shown here due to small numbers of in-hospital mortality.^[244]

Afterwards, the activity-weighted mean excess length of stay was calculated from the difference in the expected length of stay per day and the frequency of norovirus patients (Supplementary Figure 22).

Figure 22. Frequency of developing norovirus, and the expected length of stay for norovirus and control patients.



The upper panel shows how most inpatients developed norovirus during the first 10 days of their stay, while the lower panel shows the daily difference in the expected length of stay between norovirus and control patients, which remained relatively constant until around day 24.

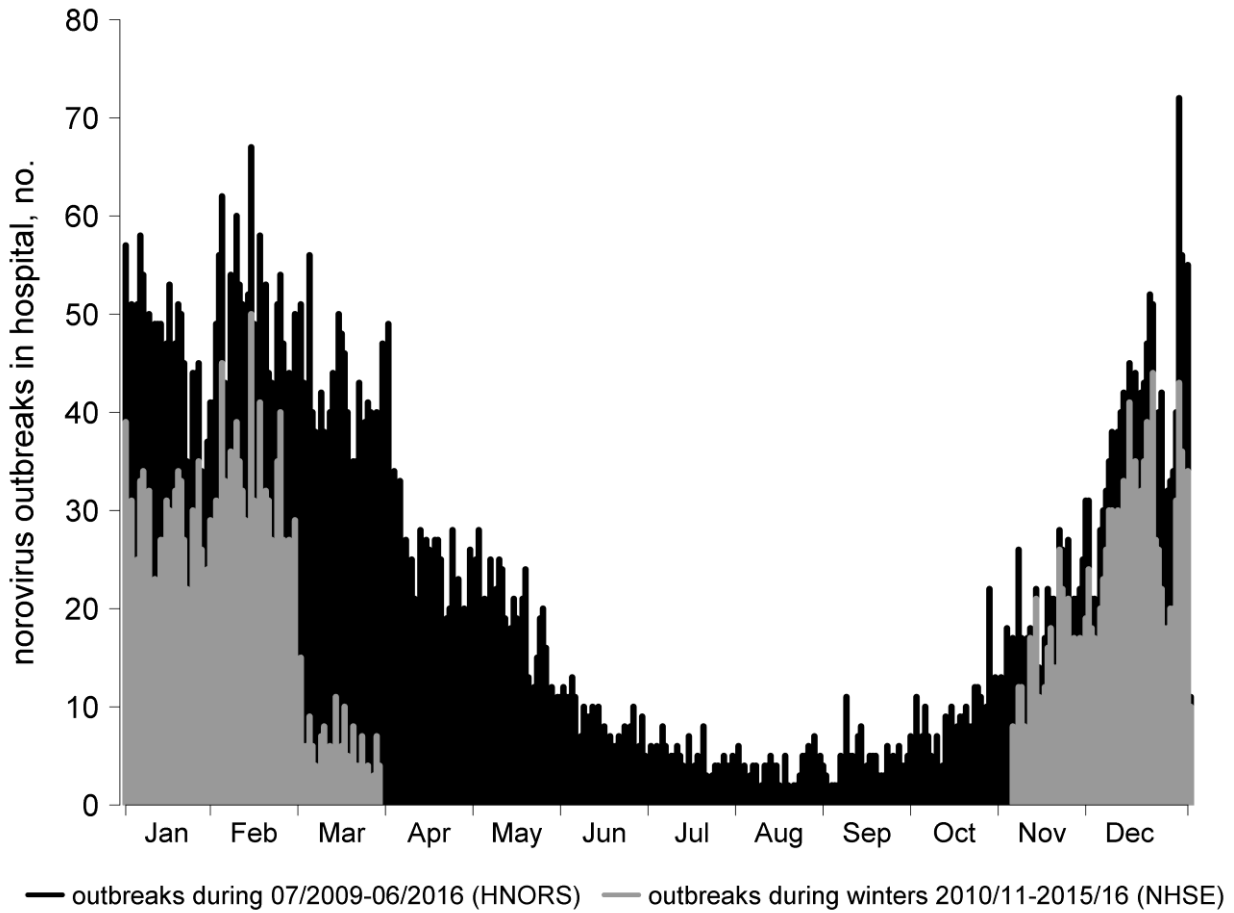
Finally, 10,000 bootstraps were ran to obtain robust estimates of the standard error to calculate 95% confidence intervals. Although relatively wide, the obtained intervals corresponded to previously published durations of symptomatic disease in hospitalised norovirus patients of 1 to 8 days.^[40,67,83,279] Moreover, the negative lower-bound confidence interval obtained for norovirus cases with primary diagnoses points towards them having left the model faster than control patients (i.e., hazard rate $\lambda_{02} < \lambda_{12}$; cf. Supplementary Figure 20), which may be explained by a short overall length of stay and fast discharge of norovirus cases when admitted for acute gastrointestinal symptoms only. Another possible explanation would be a higher in-hospital mortality of norovirus cases (i.e., $\lambda_{03} < \lambda_{13}$),^[272] which was not applicable in the sample used here.

4.10.4 Details on the comparison of bed-days kept unoccupied for infection control

For a fair comparison of the bed-days kept unoccupied due to norovirus, the figures voluntarily reported to HNORS during norovirus outbreaks were matched with those mandatorily recorded by NHS England for acute care hospitals during winters. The resulting ratio was used to scale up figures in HNORS.

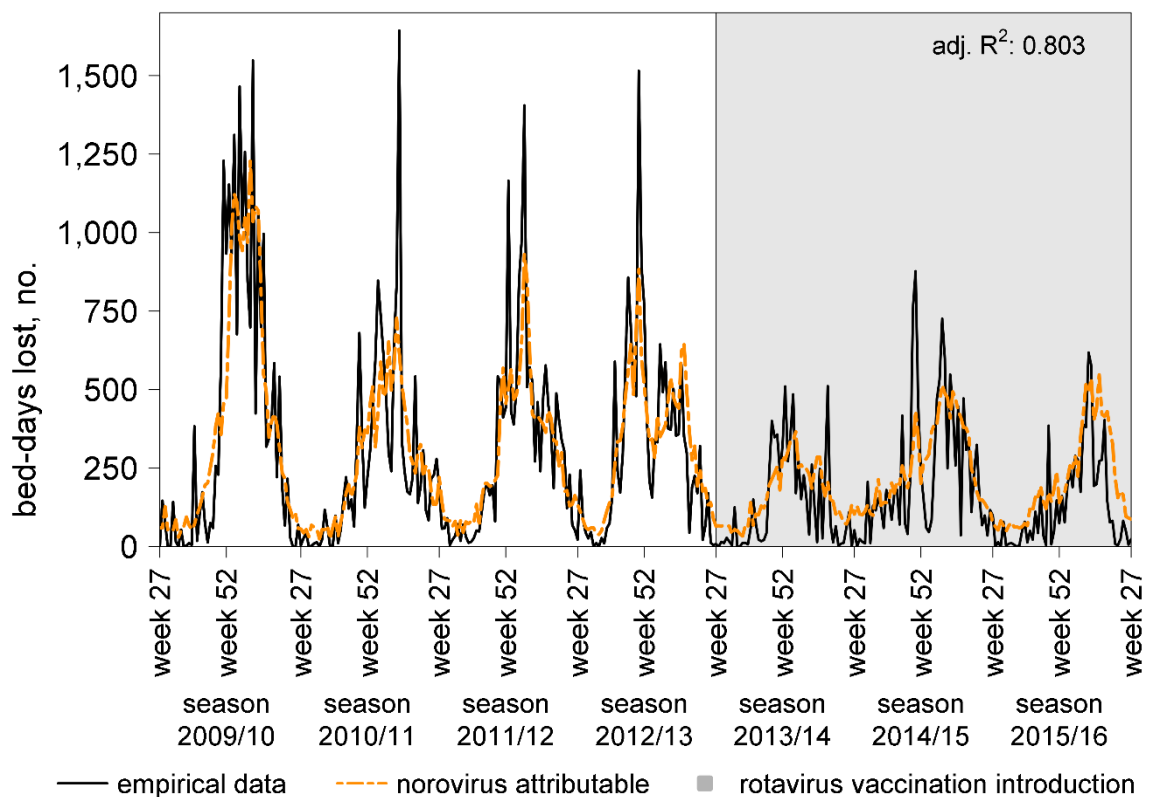
For HNORS, outbreaks were limited to those of acute care hospitals, excluded maternity and mental health wards, and restricted outbreaks to the same range of dates recorded each winter by NHS England via the start and end date of outbreaks. Thus, of the 8,142 outbreaks included in this study during July 2009 to June 2016, 39 outbreaks in community and mental health hospitals were first excluded as well as 41 outbreaks in maternity and mental health wards. Limiting the outbreaks to the same days during winters as recorded by NHS England excluded 4,803 outbreaks, of which n=1,756 belonged to the entire season 2009/10 given that NHS England started recording only in winter 2010/11. In total, 3,259 outbreaks remained for the comparison that made up for 40.4% of all outbreaks in HNORS, while the bed-days lost in those outbreaks made up for about 52% of all bed-days lost in HNORS. Figure 23 illustrates the difference between the outbreaks reported annually and the outbreaks considered during the winters of 2010/11 to 2015/16.

Figure 23. Daily number of outbreaks recorded in HNORS between July 2009 to June 2016, and of outbreaks during the same period of time as recorded by NHS England, per start date.



In addition, it was explored whether the bed-days lost recorded in HNORS were associated with norovirus by repeating the linear regression described above. Norovirus was the only covariate that was non-negative and statistically significant for predicting the number of bed-days lost in outbreaks. The adjusted R^2 is suggestive of norovirus laboratory reports being able to explain more than 80% of the bed-days lost (Supplementary Figure 24).

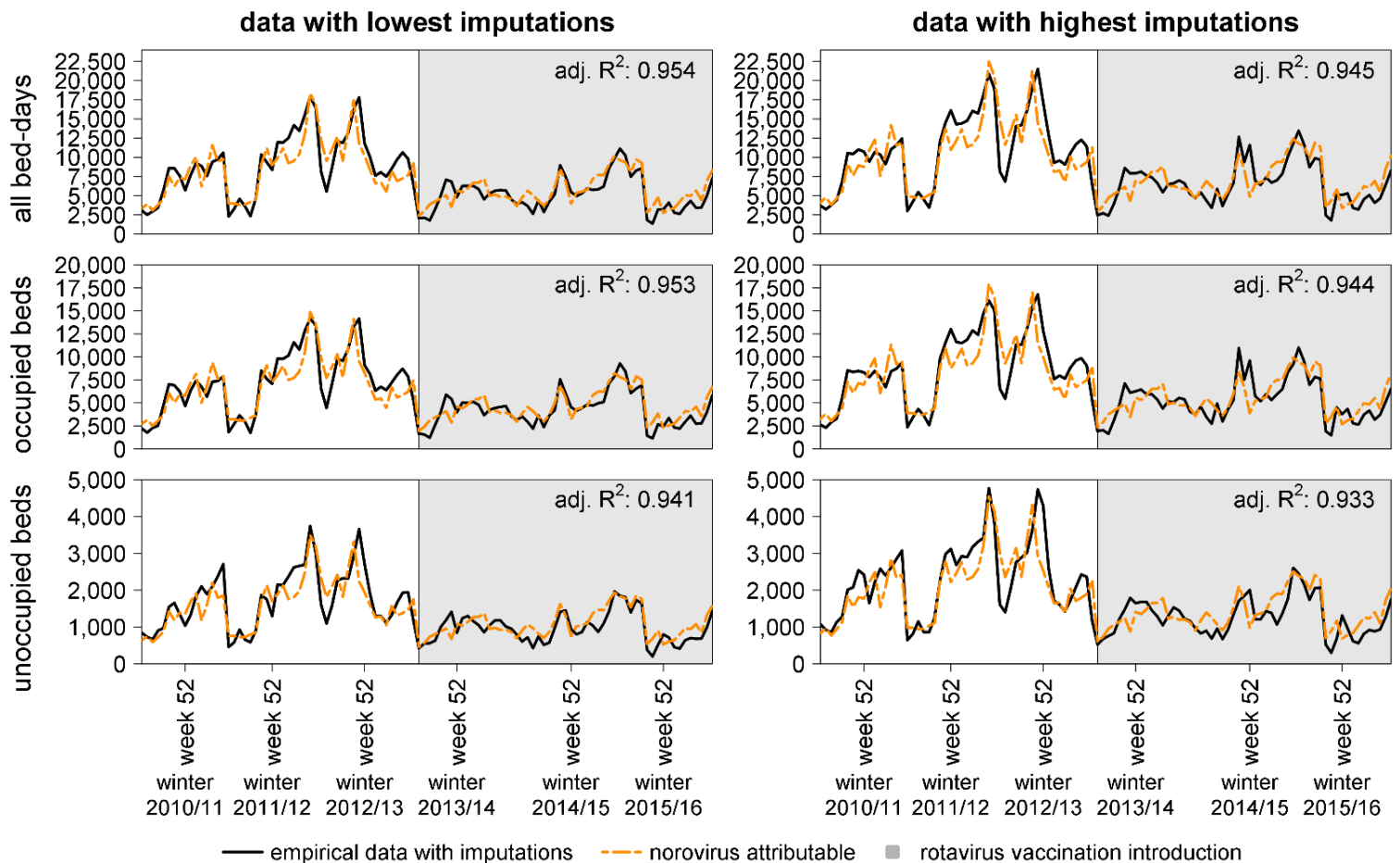
Figure 24. Weekly number of bed-days lost recorded in HNORS between July 2009 to June 2016.



For NHS England, missing values were imputed for weekends and Christmas holidays in best-to-worst-case scenarios (i.e., lowest to highest imputations).^[268] Afterwards, outbreaks were approximated using conventional definitions for norovirus ^[40,50,280] by excluding all single beds that were unavailable for merely one day within 48 hours, which reduced the 142,100–186,000 bed-days across all six winters with the lowest-to-highest imputations only marginally to 141,600–185,800 bed-days.

It was also investigated whether unavailable beds recorded by NHS England were associated with norovirus by repeating the linear regression described above. Norovirus was always the only covariate left in all regression models (including scenario analyses) that was non-negative and statistically significant for predicting the hospital bed-days closed unoccupied, occupied, and combined for both the lowest and highest imputations (Supplementary Figure 25). When calculating Pearson's correlation coefficient to investigate the linear relationship between the number of bed-days lost during outbreaks (in HNORS) and the unoccupied bed-days unavailable (by NHS England) during winters per week, positive correlations were found of $r=0.76$ for the lowest imputations and $r=0.73$ for the highest imputations.

Figure 25. Weekly number of bed-days closed due to diarrhoea and vomiting/norovirus-like symptoms recorded by NHS England during winters, 2010/11 to 2015/16.



Note the different scales for the horizontal panels.

Overall, 21.2%–28.0% of unoccupied bed-days recorded by NHS England matched the bed-days reported for outbreaks to HNORS (Supplementary Figure 26). Between July 2009 and June 2013, the number of matching bed-days was higher with 22.6%–29.7%, which decreased in subsequent years to 19.7%–26.3% between July 2013 and June 2016. Apart from the mode of reporting (i.e., voluntary to HNORS vs. mandatory to NHS England), other possible explanations for this discrepancy could be that hospitals start reporting an outbreak to HNORS but do not update their report once the outbreak has finished, which would thus not contain all numbers of bed-days lost, staff absences and patients involved. Also, hospitals may perceive both systems as duplicate; or there may be a lack of general awareness of HNORS.

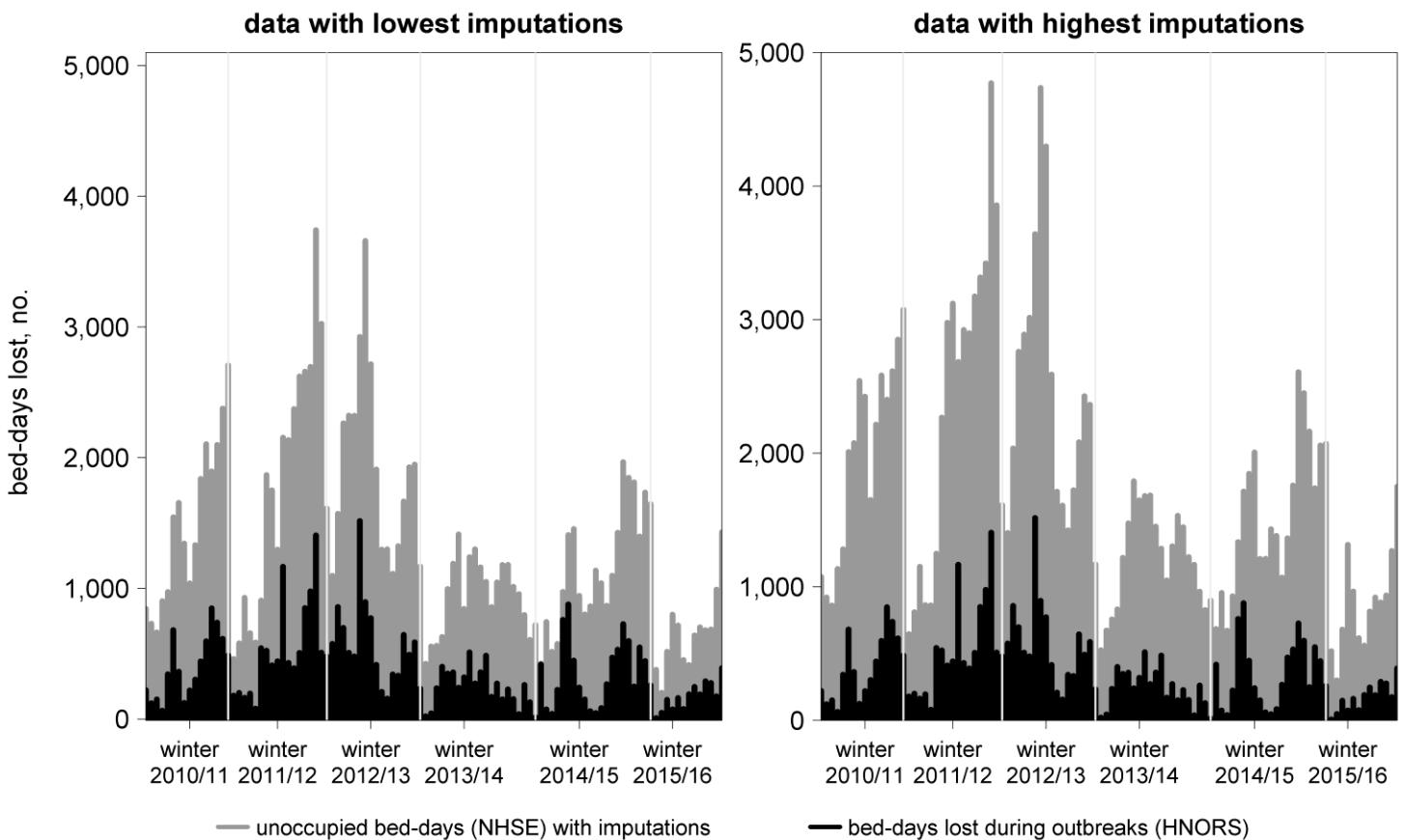


Figure 26. Matched weekly number of bed-days lost during outbreaks reported to HNORS vs. lowest and highest imputations of unoccupied bed-days recorded by NHS England, winters 2010/11 to 2015/16.

Assuming that the observed difference applied throughout the year and also to community hospitals and maternity and mental health wards, the numbers of bed-days

lost recorded in HNORS were scaled up (Supplementary Table 26). For 2009/10, the figures for across the other six winters were used given that NHS England only started recording the winter situation in 2010/11. Note that adjusting for potential under-reporting of outbreaks explicitly first before scaling up the then-higher figures of bed-days with the then-lower number of non-matching bed-days would give the same results.

Table 26. National trend of hospital bed-days lost unoccupied in England per winter, 2009/10–2015/16

Source	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
HNORS ^a	n/a	6,300	9,400	9,700	5,000	7,500	2,300
NHSE ^b	n/a	24,000– 31,700	32,000– 42,600	32,500– 41,900	19,700– 25,400	24,700– 32,600	8,600– 11,500
matching (%)	n/a	19.4–25.2	22.6–30.1	23.4–29.7	19.4–25.3	23.3–31.6	19.7–26.3
Adj. bed-days lost annually	81,700– 108,000 ^c	60,700– 78,600	57,300– 76,300	57,000– 72,400	29,200– 38,000	39,100– 53,100	27,400– 36,400

HNORS: Hospital Norovirus Outbreak Reporting System, n/a: not applicable, NHSE: National Health Service England

a: Limited to non-community hospitals, excluding maternity and mental health wards, and to the recording periods of NHSE each winter.

b: Imputed missing values for weekends and Christmas holidays in best-to-worst-case scenarios, excluded isolated beds closed without another bed closed in 48 hours in order to approximate outbreaks, and ensured association with norovirus via linear regressions.

c: Given that NHS England started recording in winter 2010/11, the six other winters were used to adjust the number for 2009/10.

4.10.5 Details on the estimated number of staff being absent during norovirus outbreaks

Potential under-reporting of the number of staff being absent during outbreaks were accounted for by multiplying the number of patients reported to HNORS with the ratio of infected patients to staff of 1:0.63 from a previous epidemiological study in one region of England that closely monitored norovirus outbreaks during April 2002 and March 2003, involving 2,154 patients and 1,360 healthcare staff.^[41] Given that the number of patients involved in outbreaks is also under-recorded due to under-reporting of outbreaks,^[259] patient figures were first scaled up to 100%. Note: The estimated number of norovirus patients was not taken as baseline given that this will overestimate staff absences, which occur only for symptomatic disease and particularly during outbreaks.

These adjustments led to figures that were about three times higher than the reported absences (Supplementary Table 27). Overall, there were an estimated median 9,100 (IQR: 5,100–12,000) individual staff absences during outbreaks annually between July 2009 and June 2016.

Table 27. Number of staff absences and patients during norovirus outbreaks in England per season.

Variable	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Patients ^a	19,500	11,500	15,500	14,000	5,400	7,700	4,300
staff absences ^a	5,200	3,000	3,700	3,500	1,400	2,100	1,300
Patients ^b	24,400	14,400	19,400	17,500	6,700	9,600	5,300
staff absences ^c	15,400	9,100	12,200	11,100	4,200	6,100	3,400

HNORS: Hospital Norovirus Outbreak Reporting System.

a: Raw data of patients and staff absences from HNORS. Raw staff absences only shown for reference here.

b: Scaled up to 100% to account for under-reporting of outbreaks.^[259]

c: Estimated by multiplying the number of patients with the ratio of patients to staff from a previous norovirus outbreak study in England.^[41]

Interestingly, there was a decrease in absences over time, which matched the decrease in reported outbreaks (Supplementary Table 20). Between July 2009 and June 2013 there were a median 12,000 (IQR: 11,000–13,000) individual staff absences, which decreased between July 2013 and June 2016 to only a median 4,200 (IQR: 3,800–5,100) staff absences. It is unclear whether this is a genuine decrease in recent seasons or a result of reporting bias, especially in light of the stable (if not slowly increasing) number of secondary norovirus-associated gastroenteritis diagnoses in England (Figure 15 in the main text).

4.10.6 Details of the costing approach

Inpatients with a primary norovirus diagnosis were costed with the activity-weighted mean reference costs for elective, non-elective, non-elective short stay and day cases of gastrointestinal infections, with or without any intervention and with any Complication and Comorbidity (CC) score (i.e., all healthcare resource group codes starting with FZ36*) and paediatric infectious or non-infectious gastroenteritis, irrespective of the CC score (i.e., all codes starting with PF21*).[243]

For inpatients with secondary diagnoses attributable to norovirus, only their excess stay due to norovirus was costed by using the activity-weighted mean excess bed-day value for elective and non-elective stays of gastrointestinal infections (all codes starting with FZ36*) and paediatric infectious or non-infectious gastroenteritis, with any Complication and Comorbidity (CC) score (all codes starting with PF21*).[243] The resource consumption of day cases was approximated with 0.5 bed-days.

For hospital bed-days kept unoccupied, the excess bed-day value for all elective and non-elective stays was used (all codes), irrespective of intervention and the CC score.[243] Excluding gastroenteritis would assume that all hospitalisations for gastroenteritis are unnecessary, which may not be true for the more severe forms.

Staff absences due to norovirus were costed using the average wage of the mid-range grade E of the NHS pay scale for nurses in England for 2015/16.[264] An estimated 3.14 days of work missed per absence was assumed based on a previous norovirus outbreak study in England involving 1,360 staff members.[41]

For the next-best alternative patients forgone, whose forgone health benefit gain poses the relevant opportunity costs for decision makers aiming to maximise population health,[260] it was assumed that the national average of the regularly admitted non-gastroenteritis patients in England were a reasonable proxy.[243,244] These alternative patients were costed with the activity-weighted mean reference costs for elective, non-elective, non-elective short stay and day cases of non-gastrointestinal diagnoses (excluding all codes starting with FZ36* or PF21*).[243]

The input parameters and the values used for multivariate sensitivity analyses are shown in Supplementary Table 28.

Table 28. Input parameters of the calculations for bed-days.

Parameter	Value (sensitivity analysis)	Unit	Description and sources
Length of stay	5.01 (3.3, 7.2)	days	Mean hospital LOS of all non-gastroenteritis cases in England (HES, 2015/16). Sensitivity analysis: Lowest and highest mean LOS per non-gastroenteritis subgroup (local hospital sample).
	3.33 (0.17, 6.50)	days	Mean excess hospital LOS of patients with norovirus infection (local hospital sample). Sensitivity analysis: 95% confidence interval.
Unit costs	£1,072 (£800, £1,222)	per patient	Mean NHS reference costs of gastroenteritis cases in England in 2015/16 (activity-weighted, only HRGs FZ36 and PF21 ^a). ^[243] Sensitivity analysis: lower and upper quartiles.
	£1,491 (£1,058, £1,766)	per patient	Mean NHS reference costs of non-gastroenteritis cases in England in 2015/16 (activity-weighted, excluding HRGs FZ36 and PF21 ^a). ^[243] Sensitivity analysis: lower and upper quartiles.
	£294 (£232, £348)	per bed-day	Mean NHS reference costs of excess bed-days for gastroenteritis in England in 2015/16 (activity-weighted, only HRGs FZ36 and PF21 ^a). ^[243] Sensitivity analysis: lower and upper quartiles.
	£306 (£220, £366)	per bed-day	Mean NHS reference costs of all excess bed-days in England in 2015/16 (activity-weighted, all HRGs). ^[243] Sensitivity analysis: lower and upper quartiles.
Norovirus-attributable gastroenteritis	0.124 (0.118, 0.133)	proportion	Estimated from cases with primary gastrointestinal diagnoses between July 2009 and June 2013. Sensitivity analysis: 95% confidence interval.
	0.177 (0.156, 0.216)	proportion	Estimated from cases with primary gastrointestinal diagnoses between July 2013 and June 2016. Sensitivity analysis: 95% confidence interval.
	0.202 (0.177, 0.247)	proportion	Estimated from cases with secondary gastrointestinal diagnoses between July 2009 and June 2013. Sensitivity analysis: 95% confidence interval.
	0.238 (0.206, 0.299)	proportion	Estimated from cases with secondary gastrointestinal diagnoses between July 2013 and June 2016. Sensitivity analysis: 95% confidence interval.
Variable costs	0.15 (0.04, 0.34)	proportion	Estimated proportion of variable costs on total hospital costs. ^[266] Sensitivity analysis: range of proportions published for 16 medical specialties. ^[266]
QALY gain	0.239 (0.142, 0.260)	per patient	Mean (discounted) QALYs gained from hospital treatment for non-gastroenteritis cases with chronic conditions (local hospital sample, n=871). Sensitivity analysis: Mean (discounted) QALYs gained of all patients without gastroenteritis (n=2,465) and with acute life-threatening conditions (n=537), respectively. Acute life-threatening conditions were included as extreme scenario only as it seemed unrealistic to assume forgoing them constantly.

Monetary value for QALYs	£20,000 (£13,000, £30,000)	per QALY	NICE reference case. ^[267] Sensitivity analysis: estimated from mortality data, ^[281] and NICE's upper-bound threshold. ^[267]
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HES: hospital episode statistics, HRG: healthcare resource group, LOS: length of stay, NHS: National Health Service, NICE: National Institute for Health and Care Excellence, QALY: quality-adjusted life year.

a: HRG FZ36*: gastrointestinal infections; HRG PF21*: paediatric, infectious or non-infectious gastroenteritis

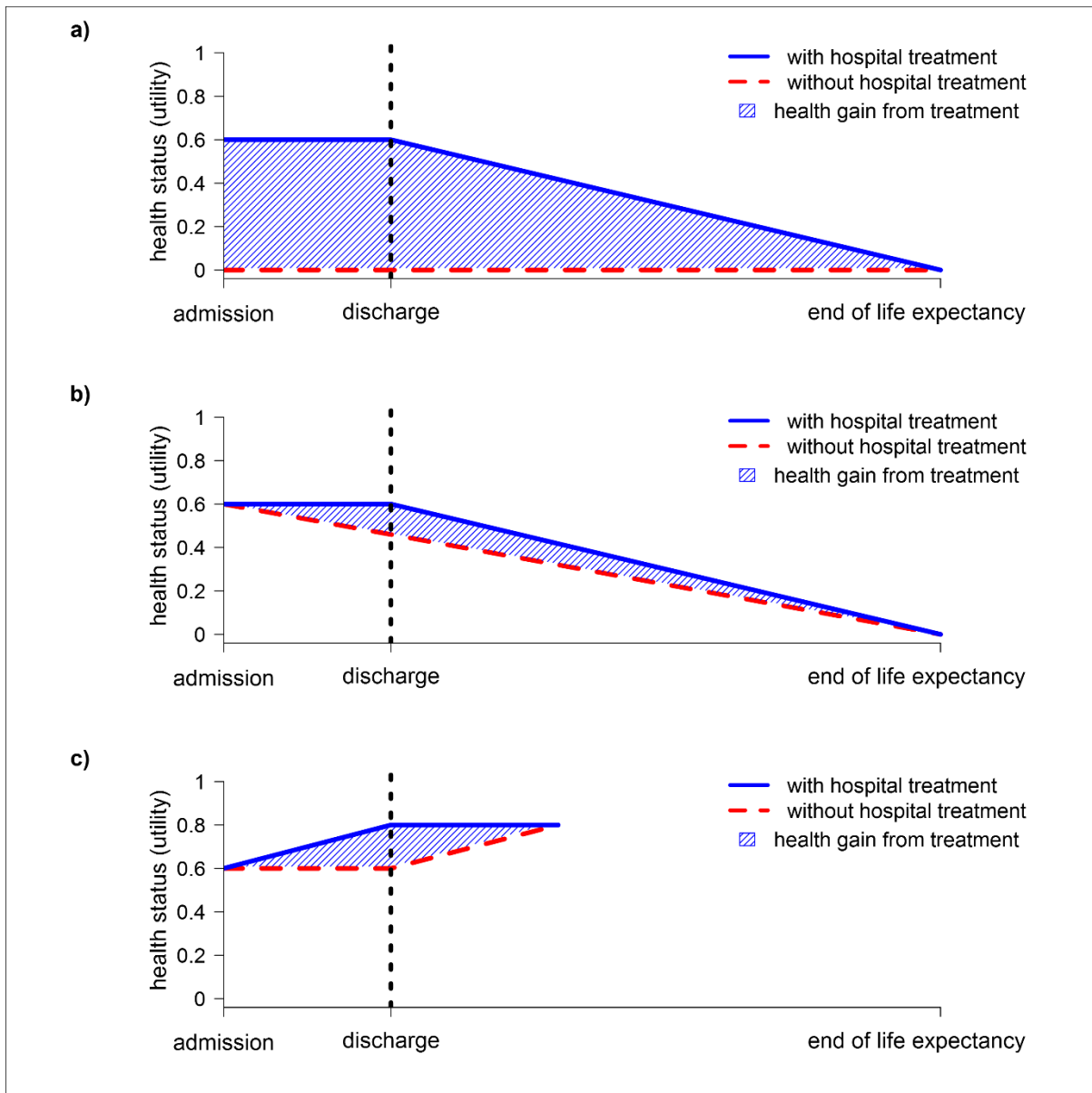
4.10.7 Details on the modelled health gain expected from hospital treatment

In the absence of national data on the health gain from hospital treatment, the expected mean quality-adjusted life years, QALYs, were estimated from individual patient-level data of a local teaching hospital in London, UK. Mean age- and sex-specific health utilities for diseased individuals were mapped to the primary admission code,^[282] and patients were separated into three sub-groups based on all diagnosis codes and the Charlson comorbidity index ^[283] (Supplementary Figure 27):

- a) For patients with acute life-threatening conditions (i.e., myocardial infarctions, congestive heart failures, and cerebrovascular diseases), immediate death was assumed without hospital treatment. With treatment, the health status was assumed to be stabilised and the utility score maintained until discharge, at which point the utility was assumed to gradually decline over the remaining age- and sex-specific life expectancy using life-tables for England.^[284]
- b) For all other patients with chronic conditions (i.e., Charlson index > 0 but not acutely life-threatening), a steady decline of the health utility for the remainder of the life expectancy was assumed without treatment, while with treatment the same assumption was made as before of an initially stabilised health status before deterioration commences after discharge.
- c) For patients without chronic or life-threatening conditions, a gradual recovery was modelled until discharge, while a delay in recovery was assumed without treatment, lasting for the entire stay in hospital, after which patients make a natural recovery over the same period of time as with hospital treatment. No difference attributable to this hospital stay was assumed for the remaining life expectancy. For the recovered health status, utility norms published sex-specifically by Programme Budget Categories were used.^[281] For 40 young patients, this non-age-specific utility norm was smaller than the age-specific diseased utility, for who a norm of 1 was thus assumed. Alternatively, one could have assumed a utility norm value of 1 for the recovered health status in line with theory, which were to skew results upwards while ignoring the patients' age, sex, and diseased utility (and thus dismissed by us).

For patients with chronic or life-threatening conditions the age- and sex-specific life expectancy from the Office for National Statistics was used.^[284] For all cases of in-hospital mortality, QALYs were calculated using the observed survival time.

Figure 27. Health gain in terms of quality-adjusted life years, QALYs, from hospital treatment vs. no hospital treatment.



To account for potential heterogeneity, the health gain modelling differed for the three patient sub-groups of a) acute life-threatening conditions, b) chronic conditions, or c) none of these conditions. a) Patients with acute life-threatening conditions survive with hospital treatment for their remaining age- and sex-specific life expectancy. b) Patients with chronic conditions maintain their health at a higher level with hospital treatment for their remaining age- and sex-specific life expectancy. c) Patients with none of these conditions recover faster with hospital treatment, but there is no effect attributable to this hospital stay for the remaining life expectancy.

4.10.8 Details on results of the burden and costs estimation

Table 29 shows the results of the burden estimation for patients, bed-days and staff absences per season.

Table 29. Results for the burden of norovirus-associated gastroenteritis in hospital in England per season, 2009/10-2015/16

Variable	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Patients							
~ with primary norovirus diagnosis (95% CI) ^a	28,200 (26,800–30,200)	27,300 (26,000–29,300)	28,900 (27,500–31,000)	30,700 (29,200–32,900)	40,100 (35,300–48,900)	41,900 (36,900–51,100)	40,800 (36,000–49,800)
~ with secondary norovirus diagnosis (95% CI) ^b	44,600 (39,100–54,600)	44,300 (38,800–54,200)	46,200 (40,500–56,500)	49,100 (43,000–60,000)	55,900 (48,400–70,200)	61,500 (53,300–77,300)	63,600 (55,000–79,800)
total (95% CI)	72,800 (65,900–84,800)	71,600 (64,800–83,500)	75,100 (68,000–87,500)	79,800 (72,200–92,900)	96,000 (83,700–119,000)	103,000 (90,200–128,000)	104,000 (91,000–130,000)
Bed-days							
~ used for primary norovirus diagnoses (95% CI) ^a	70,500 (67,100–75,600)	62,900 (59,900–67,500)	61,400 (58,400–65,900)	62,900 (59,900–67,500)	81,400 (71,700–99,300)	83,500 (73,600–102,000)	76,800 (67,700–93,800)
~ used for secondary norovirus diagnoses (95% CI) ^c	135,000 (118,000–165,000)	132,000 (116,000–162,000)	136,000 (119,000–167,000)	146,000 (128,000–178,000)	165,000 (143,000–207,000)	181,000 (157,000–227,000)	185,000 (160,000–233,000)
~ lost unoccupied, lowest-to-highest imputations ^d	81,700–108,000	60,700–78,600	57,300–76,300	57,000–72,400	29,200–38,000	39,100–53,100	27,400–36,400
total, low imputations (95% CI)	287,000 (267,000–322,000)	256,000 (236,000–290,000)	255,000 (235,000–290,000)	266,000 (245,000–303,000)	275,000 (244,000–336,000)	304,000 (269,000–368,000)	290,000 (255,000–354,000)
total, high imputations (95% CI)	313,000 (293,000–348,000)	274,000 (254,000–308,000)	274,000 (254,000–309,000)	281,000 (260,000–318,000)	284,000 (252,000–345,000)	318,000 (283,000–382,000)	299,000 (265,000–363,000)
Staff absences due to illness							
total ^e	15,400	9,100	12,200	11,100	4,200	6,100	3,400

HES: hospital episode statistics, HNORS: Hospital Norovirus Outbreak Reporting System, LOS: length of stay, NHS: National Health Service.

- a: Derived from inpatients with a primary diagnosis of gastroenteritis attributed to norovirus with the two regression models with the highest goodness-of-fit for prior and after mid-2013.
- b: Derived from inpatients with a secondary diagnosis of gastroenteritis attributed to norovirus with the two regression models with the highest goodness-of-fit for prior and after mid-2013.
- c: Derived from the non-day cases with a norovirus-attributable secondary diagnosis of gastroenteritis times the estimated excess length of stay due to norovirus of 3.33 (95%-CI: 0.17–6.50) days plus the number of day cases with a norovirus-attributable secondary diagnosis of gastroenteritis times the approximated resource consumption of 0.5 bed-days.
- d: Figures of bed-days lost were scaled up using the ratios derived from the comparison of bed-days during winters reported voluntarily to HNORS versus mandatorily to NHS England.
- e: Figures account for under-reporting of outbreaks, and absences during outbreaks.

Table 30 shows the costing results, split up for the conventional costing and the opportunity costing of bed-days.

Table 30. Results for the costs of norovirus-associated gastroenteritis in hospital in England per season, 2009/10-2015/16

Variable	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Conventional costing							
Patients with primary norovirus diagnosis, in million £ (95% CI) ^a	30.2 (21.4–36.9)	29.3 (20.8–35.8)	31.0 (22.0–37.9)	32.9 (23.4–40.2)	43.0 (28.3–59.7)	44.9 (29.5–62.4)	43.8 (28.8–60.9)
Bed-days used for secondary norovirus diagnoses, in million £ (95% CI) ^b	39.5 (27.3–57.4)	38.8 (26.8–56.3)	40.0 (27.7–58.0)	42.8 (29.6–62.1)	48.4 (33.1–72.1)	53.2 (36.3–79.2)	54.4 (37.1–81.1)
Bed-days lost unoccupied, low-to-high imputations, in million £ ^c	25.0–33.0	18.6–24.0	17.5–23.3	17.4–22.1	8.9–11.6	12.0–16.2	8.4–11.1
Staff absence costs due to illness, in million £ ^d	4.9	2.9	3.9	3.5	1.3	1.9	1.1
Total, low-to-high imputations, in million £	99.6–107.6	89.5–95.0	92.4–98.2	96.7–101.4	101.6–104.3	111.9–116.2	107.6–110.4
Opportunity costing							
Patients forgone, low-to-high	57,300–62,500	51,100–54,600	50,900–54,700	53,100–56,100	55,000–56,700	60,600–63,400	57,800–59,600
QALYs forgone, low-to-high	13,700–14,900	12,200–13,100	12,200–13,100	12,700–13,400	13,100–13,600	14,500–15,200	13,800–14,200
Net monetary benefit, low-to-high, in million £ ^e	188.4–205.7	168.0–179.7	167.4–179.9	174.6–184.7	180.9–186.7	199.4–208.6	190.1–196.1

HES: hospital episode statistics, HNORS: Hospital Norovirus Outbreak Reporting System, LOS: length of stay, NHS: National Health Service.

a: Patients with primary diagnoses were costed directly using NHS reference costs.^[243]

b: Patients with secondary diagnoses were not costed directly given that they were in hospital for other primary reasons. Instead, their excess bed-days due to norovirus were costed.

c: Figures of bed-days lost were scaled up using the ratios derived from the comparison of bed-days reported during winters to HNORS vs. NHS England.

d: Figures account for under-reporting of outbreaks, and absences during outbreaks.

e: Equivalent to opportunity costs, unless a higher net benefit was achievable with the alternative patients forgone than with the norovirus patients.

The net monetary benefit of the QALYs forgone is equivalent to the opportunity costs of the norovirus patients, unless a higher net benefit was achievable with the alternative patients forgone.^[260] In order to investigate this, this study costed the QALY gain of norovirus patients with a primary diagnosis (0.078; Table 18) and a secondary norovirus diagnoses, for which the gastroenteritis-related health gain was approximated by subtracting the QALY gain of control patients with no primary gastroenteritis diagnosis and no norovirus infection from the QALY gain of inpatients with no primary gastroenteritis diagnosis but norovirus infection (i.e., $0.211-0.142=0.069$; cf. Table 18 and Supplementary Table 21). The results of this analysis are shown in Table 31, which estimated that norovirus patients gained from hospital treatment an expected number of 5,400 QALYs before July 2013 and 7,500 QALYs after July 2013.

Table 31. Costing results for the bed-days used for norovirus-associated inpatients in England, 2009/10-2015/16

	Before July 2013: 261,000 bed-days		After July 2013: 290,000 bed-days		Across seasons: 275,000 bed-days	
	Norovirus cases, n=73,900	Forgone patients: n=52,100	Norovirus cases, n=103,400	Forgone patients: n=57,800	Norovirus cases, n=79,800	Forgone patients: n=55,000
Expenditure (£ million in total)	94.5	77.6	107.6	86.1	99.6	82.0
Benefit (GMB, £ million in total)	107.2	248.9	150.2	276.2	115.6	262.8
Net benefit (NMB, £ million in total)	12.7	171.3	42.6	190.1	16.0	180.9
Economic costs (£ million in total) ^a	265.5	90.3	297.7	128.7	282.5	98.0

GMB: gross monetary benefit (i.e., QALYs gained times £20,000^[267]), NICE: National Institute for Health and Care Excellence, NMB: net monetary benefit (i.e., benefit-expenditure), QALY: quality-adjusted life year.

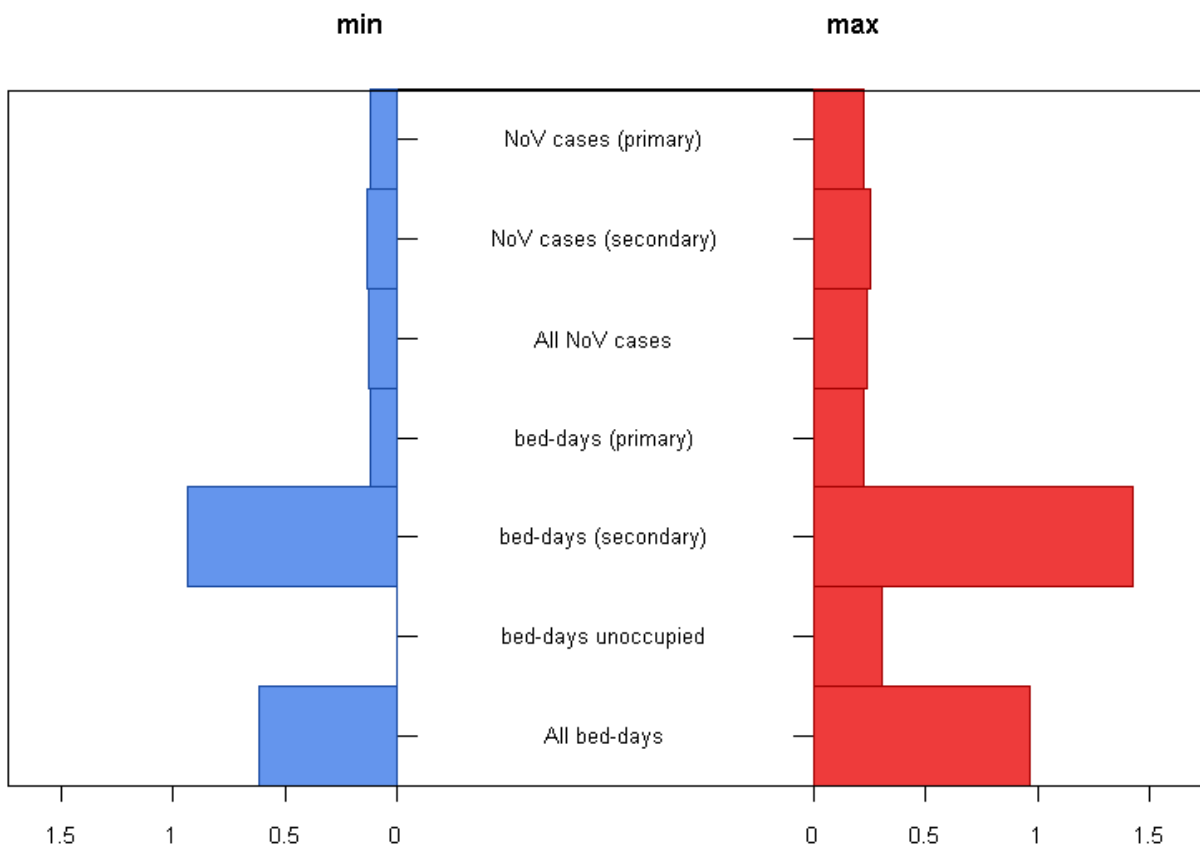
a: Economic costs are defined as the expenditure incurred plus the highest net monetary benefit forgone; they approximate to opportunity costs in case the chosen option was the sub-optimal alternative.

The net monetary benefit of the forgone patients was always higher than that of norovirus patients, and the economic costs were always lower than the benefit for norovirus only (Supplementary Table 31). As such, the higher net benefit was achievable with the forgone patients, rendering the norovirus cases as sub-optimal treatment choice from an economic perspective aiming to maximise population health. Consequently, the economic costs approximate to opportunity costs here.

4.10.9 Details on the sensitivity analysis

For the burden estimation, the estimated confidence intervals of the best-fitting regression models were used to obtain lower and upper estimates for the norovirus-attributable cases and the bed-days of primary diagnoses, and the estimated confidence interval of the excess length of stay due to norovirus from the multi-state model were used. Due to the wide confidence interval of the excess hospital stay of norovirus cases, the bed-days used for them showed the highest uncertainty to either side of the base case value (Supplementary Figure 28). For the bed-days lost unoccupied for infection control, the lower value was taken as conservative estimate, which is why there is only an upwards trend shown (Supplementary Figure 28); the actual number of bed-days kept unoccupied is likely higher than assumed here but also lower than the worst-case scenario.

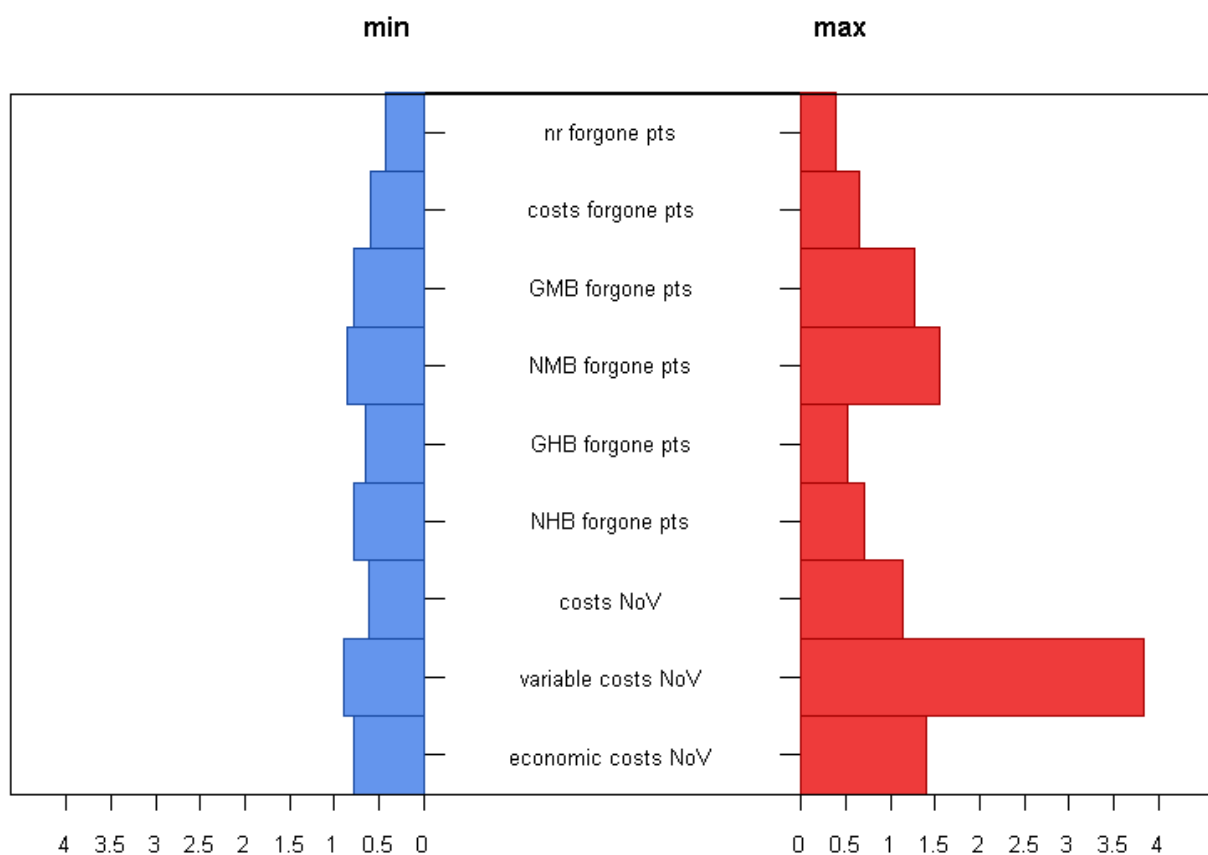
Figure 28. Tornado diagram of the change (in %) of the base estimates for the burden estimation.



NoV: norovirus.

For the costs, estimates appeared to be right-skewed, as is often the case for cost data.^[4] There appeared to be less uncertainty surrounding calculations using the length of stay and expenditure of the forgone alternative patients (Supplementary Figure 29: “nr forgone pts”, “costs forgone pts”) than for calculations relying on a monetary value for the quality-adjusted life years, QALYs, gained (Supplementary Figure 29, “GMB forgone pts”, “NMB forgone pts”, “economic costs NoV”). For the variable costs proportion of the expenditure on norovirus (“variable costs NoV”), the wide interval chosen as input of up to 0.34 is reflecting the large uncertainty surrounding the estimate when the total expenditures also increased.

Figure 29. Tornado diagram of the change (in %) of the base estimates for the cost calculation.



GHB: gross health benefit, GMB: gross monetary benefit, NHB: net health benefit, NMB: net monetary benefit, NoV: norovirus, pts: patients.

4.11 ADDITIONAL RESULTS FOR THE OTHER APPROACHES IDENTIFIED

In order to streamline the discussion of the costing approach for a clinical audience, the results presented in the paper in chapter 4 focussed on the comparison of the conventional costing approach and the novel opportunity costs approach. Here, the implications for costing are discussed using all 14 approaches presented in chapter 2 (see Table 32 for a summary).

First, following Methodology A showed that while the bed-days used for norovirus were only valued as an expected 57,800 patient-equivalents (approach 1), the expenditure on norovirus was valued as an expected 72,200 treatment-equivalents (approach 2). This difference in the result when using the exchange rate between natural units (approach 1) or the exchange rate between the expenditures associated with the natural units (approach 2) is largely explained by the fact that the amount of money that could have been spent on the treatment of alternative patients included the costs of day cases, which do not use many bed-days but incur expenditures, and staff absence costs (although these account for merely 3%). However, when aiming to maximise throughput it seems as if the expenditure was able to buy more treatments than the beds would allow treating. As a result, chapter 4 disregarded treatment-equivalents for its ease in resulting in distorted values, particularly when looking over time (cf. section 2.5.4), while the average length of stay in hospital for patients in England has stayed relatively constant over the last years,^[244] suggesting a plateau may have been reached, and its use seems preferable.

Second, Methodology B gave vastly different values for the opportunity costs of bed-days with the different approaches for both the valuation in terms of money as well as the health benefit (i.e., QALYs), with the treatment-equivalents giving generally higher values than the patient-equivalents (including the gross monetary benefit for the treatment-equivalents, which would have resulted in £345.2 million). The lowest results were obtained for the direct expenditures on the alternative patients (approach 3a), and the highest for the gross monetary benefit of the patients forgone (approach 5). Interestingly, the universal measure for the expected next-best use of £20,000 per QALYs gave the lowest QALYs (approach 6), while the gross health benefit for the second-best patients gave the highest (approach 4). Of note, approaches from the provider perspective that required information on their revenue (cf. section 2.5.2.2) have not been calculated

on the national level in the absence of available data, given that the reimbursement levels are determined in England based on the average accounting expenditures of all providers.

Third, Methodology C calculated expenditures according to conventional practices, assuming that the expenditure signals the amount of money that could have been employed in its second-best alternative use (approach 7). This amount is not indicative of monetary savings in case all norovirus cases were averted, but the amount that could have been used alternatively (cf. section 2.5.1). Looking at the variable cost proportion may give an idea of the actual cash savings (approach 8), which will mostly be saved on staff absences and cautionary measures given that no treatment for norovirus exists as of now (cf. section 1.3.2).

Lastly, Methodology D is not sensible to be looked at in isolation as it intends to correct for having chosen the sub-optimal alternative in terms of net benefits (cf. section 2.5.1); for a complete overview of the results for the patient chosen and the highest valued alternative forgone see section 4.10.8. In situations where it proves impossible to determine the optimal alternative or disprove an alternative as not optimal, it may be preferable to consider only the net monetary benefit of the second best patients (approach New1) and qualitatively acknowledge the distortion in its value from market imperfections.

Table 32. Overview of approaches to value the opportunity costs of the bed-days used by the norovirus cases

Approach	Description	Equation	Results
<i>Methodology A: Units of the second-best alternative forgone</i>			
1	Patient-equivalents forgone	$LOS_i * \frac{1}{LOS_j} (* OCR)$	57,800
2	Treatment-equivalents forgone	$C_i * \frac{1}{C_j}$	72,200
<i>Methodology B: Net benefit of the second-best alternative forgone</i>			
<i>Valuation in terms of money</i>			
3a	Expenditure forgone on patient-equivalents	$LOS_i * \frac{C_j}{LOS_j}$	£86,100,000
3b	Revenue forgone from the patient-equivalents	$LOS_i * \frac{R_j}{LOS_j} (* OCR)$	n/a
3c	Net revenue forgone from the patient-equivalents	$LOS_i * \frac{(R_j - C_j)}{LOS_j}$	n/a
5	Gross monetary benefit forgone for the patient-equivalents	$LOS_i * \frac{(B_j * \lambda)}{LOS_j}$	£276,200,000
New1	Net monetary benefit forgone for the patient-equivalents	$LOS_i * \frac{(B_j * \lambda - C_j)}{LOS_j}$	£190,100,000
New2	Net monetary benefit forgone for the treatment-equivalents	$C_i * \frac{(B_j * \lambda - C_j)}{C_j}$	£237,500,000
<i>Valuation in terms of QALYs</i>			
4	Gross health benefit forgone for patient-equivalents	$LOS_i * \frac{B_j}{LOS_j}$	13,800
6	Health benefit forgone for expected second-best use	$C_i * \frac{1}{\lambda}$	5,400
New3	Net health benefit forgone for the patient-equivalents	$LOS_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{LOS_j}$	9,500
New4	Net health benefit forgone for the treatment-equivalents	$C_i * \frac{(B_j - (\frac{C_j}{\lambda}))}{C_j}$	11,900
<i>Methodology C: Expenditure of the alternative chosen</i>			
7	Expenditure for the resource consumption incurred	$LOS_i * \frac{C_i}{LOS_i}$	£107,600,000
8	Separating variable expenditure and non-monetary resource consumption	$LOS_i * \frac{VC_i}{LOS_i} \& LOS_i$	£16,100,000
<i>Methodology D: Expenditure of the alternative chosen + highest net benefit forgone</i>			
9	Expenditure incurred + highest net revenue forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(R_j - C_j)}{LOS_j} \right)$	n/a
New5	Expenditure incurred + highest net monetary benefit forgone	$LOS_i * \left(\frac{C_i}{LOS_i} + \frac{(B_j * \lambda - C_j)}{LOS_j} \right)$	£297,700,000

B: (health) benefit gained per patient, C_i : total expenditure incurred for i , C_j : expenditure incurred per patient, λ : monetary value assigned to QALYs in local cost-effectiveness thresholds, LOS_i : total bed-day consumption of i , LOS_j :

length of stay per patient, n/a: not available, OCR: occupancy rate, QALY: quality-adjusted life year, R: revenue per patient, VC: variable cost proportion of the expenditure.

5 NOROVIRUS OUTBREAKS IN HOSPITAL AND THE ADDITIONAL IMPACT ON BED PRESSURES

Previously, chapter 3 looked at the hospital bed pressure in winter resulting from cases with acute gastroenteritis/norovirus-like symptoms, and chapter 4 illustrated for norovirus the impact of the different costing approaches on burden of disease estimations, as predicted in chapter 2. Up to three times higher opportunity cost values were obtained for norovirus nationally when considering the alternative patients forgone who were unable to be admitted due to beds being unavailable.

Next, chapter 5 looks at the sustained transmission of norovirus during outbreaks in hospital when accounting for individuals being susceptible to illness and/or infection. It also estimates the daily risk of an inpatient becoming infected with norovirus per ward per year. Lastly, this chapter explores the additional impact of norovirus outbreaks on bed pressures from increased bed occupancy rates, which are already at high levels in many settings but especially in England.

Title of paper, name of authors and affiliations:

Norovirus outbreaks and hospital bed occupancy levels in England:

A mathematical modelling study

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Publication status: draft. Additional material that is not intended to be part of the journal submission is presented in section 5.8.1.

5.1 COVER SHEET OF RESEARCH PAPER 4

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Student	Frank Sandmann
Principal Supervisor	Prof. Mark Jit
Thesis Title	The true cost of epidemic and outbreak diseases in hospitals

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	
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Where is the work intended to be published?	not yet determined
Please list the paper's authors in the intended authorship order:	FG Sandmann (me), SR Deeny (associate supervisor), JV Robotham (associate supervisor), WJ Edmunds (advisory committee), M Jit (main supervisor)
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall concept of the model of this study, wrote the programming code of the model, performed the analysis, interpreted results, and drafted the manuscript. SRD, JVR, WJE, and MJ provided critical comments on the overall concept, analysis, interpretation of results, and the manuscript.
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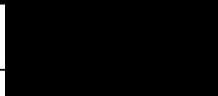
	All authors contributed to conceiving the study. I gave a preliminary presentation of this study at the Conference of Infectious Disease Dynamics (Ambleside, 2017).
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Student Signature:



Date: 27.01.2018

Supervisor Signature:



Date: 27.01.2018

5.2 ABSTRACT

Background: Hospital outbreaks of norovirus recurrently lead to bed shortages from sustained transmission among susceptible inpatients on the wards. With the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England/Improvement having recently proposed hospital bed occupancy levels of below 90% and 92%, respectively, we aimed to explore the impact of norovirus outbreaks on achieving these levels.

Methods: We built a stochastic transmission-dynamic model of norovirus outbreaks in hospital wards that accounted for individuals being susceptible to illness and/or infection. In the baseline without norovirus, stochastic admissions and discharges were simulated for typical hospital wards of the NHS in England, with mean capacities of 19.8 beds (standard deviation 6.2 beds) and occupancy rates of 89.0%.

Results: The model predicted a mean incidence of 1.46 (95%-CI: 1.38-1.54) norovirus outbreaks per ward annually, which lasted for 8.3 days and consumed 10.9 bed-days. In the majority of simulations (76.9%), the infection did not spread beyond the index case and cause outbreaks. In the baseline, the ward occupancy reached full capacity on 101 days a year (27.8%; range 34-206 days). With norovirus, occupancy levels increased by a mean of 8.1% (i.e., 1.6 longer staying inpatients). Full capacity was exceeded in 46.7% of outbreaks, with a mean 1.5 (range 0—12) new admissions waiting for free beds.

Conclusions: In England, norovirus outbreaks add to existing bed pressures and impact the admission of new patients. Recently proposed bed occupancy levels are regularly exceeded. Future research should consider the impact on health outcomes.

5.3 INTRODUCTION

Norovirus outbreaks in hospital regularly lead to bed pressures from sustained transmission among susceptible inpatients on the wards, particularly in winter when the number of outbreaks peaks.^[71,285] However, not all infections with norovirus in hospital will result in outbreaks, which are defined by more than one case connected in time and place.^[40,50,280] Moreover, not all infections will be discovered owing to mild or sub-clinical illness, which could result in asymptomatic transmission, as well as under-reporting due to hospitals not confirming all norovirus-suspected inpatients in the laboratory, miscoding cases as non-infectious, or discharging patients before gastrointestinal symptoms have developed.

Hospital outbreaks add to periodic bed crisis by increasing the occupancy levels temporarily when infected inpatients cannot be discharged, and other beds need to be kept empty for infection control. In general, while high occupancy of hospital beds can be an efficient use of health care resources, they may also be a major cause for concern.^[286] Existing observational studies suggest that high occupancy levels increase the risk of in-hospital mortality, hospital-acquired infections, excess length of stays, 30-day readmissions, and delays for other patients awaiting admission.^[286,287]

In England, the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England/Improvement have recently proposed hospital bed occupancy levels of below 90%^[287] and 92%^[288], respectively, while the National Audit Office (NAO) has noted that mean occupancy levels above 85% may lead to “regular bed shortages, periodic bed crises and increased numbers of hospital-acquired infections”.^[286]

In reality, the annual occupancy level of all general and acute hospital beds of the National Health Service (NHS) in England has increased from a mean 87.1% in 2010/11 to a mean 90.3% in 2016/17.^[289] The situation regularly worsens during winter, with occupancy levels above 91% in 2015/16 and 2016/17,^[289] and even reaching a mean 93.9% in the winter of 2017/18 (as of 18 January 2018).^[290]

The aims of this study were threefold. First, we built a stochastic transmission-dynamic model to simulate norovirus outbreaks and investigate the sustained transmission of norovirus among susceptible inpatients. Second, the model was used to determine the daily risk for hospital wards of an inpatient becoming infected with norovirus, taking into account that not all infections will lead to outbreaks. Third, we investigated the impact of

norovirus outbreaks on hospital bed occupancy levels, both of which peak during winter, for which we nested the transmission-dynamic model within a simple stochastic model of admissions and discharges for typical hospital wards in England.

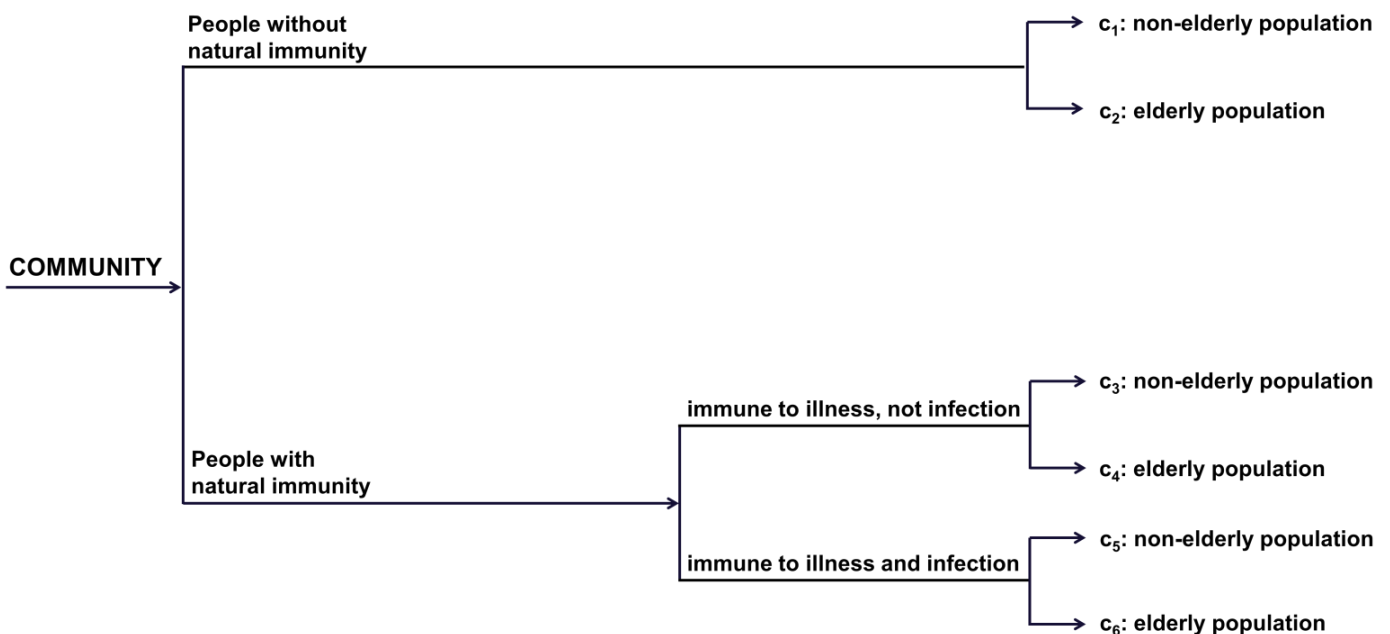
5.4 METHODS

5.4.1 Model structure

5.4.1.1 Classification tree for the general community at risk of being admitted

In the model, individuals were admitted to the hospital wards directly from the general community. The population was stratified into two age groups of <65 and ≥ 65 years, given the higher risk of hospitalisation for the elderly in England.^[244] In addition, individuals were further stratified according to whether or not they have natural immunity against norovirus infection and/or illness (Figure 30).

Figure 30. Classification tree of individuals in the community stratified by age and the natural immunity to norovirus infection or illness.



5.4.1.2 Hospital ward model: Baseline without norovirus

For the baseline situation of hospital bed occupancy without norovirus outbreaks, a typical hospital ward was modelled with bed capacity drawn from a log-normally distributed random variable with mean 19.8 beds (standard deviation 6.2 beds) based on a sample of 171 inpatient wards in England (see Appendix in section 5.8).^[41] In addition, we considered extra space for trolley beds (e.g. in hallways) of 10% of the bed capacity. The occupancy was simulated using the national mean bed-occupancy rate in 2015 of 0.890.^[291] Seasonal demand in bed-days was accounted for with a cosine function fitted to the national hospital bed occupancy data (see Appendix in section 5.8).^[291]

Individuals in the community were randomly admitted each day following a Poisson distribution. Based on the classification tree for the community (Figure 30), we distinguished three potential inpatient admission groups:

- i. Admissions not immune but susceptible to norovirus infection and illness ($c_1 + c_2$);
- ii. Admissions immune to illness but not norovirus infection ($c_3 + c_4$);
- iii. Admissions immune to illness and norovirus infection ($c_5 + c_6$).

Each day, inpatients were discharged according to a Poisson distribution, conditional on the number of inpatients in each admission group on the previous day ($t-1$).

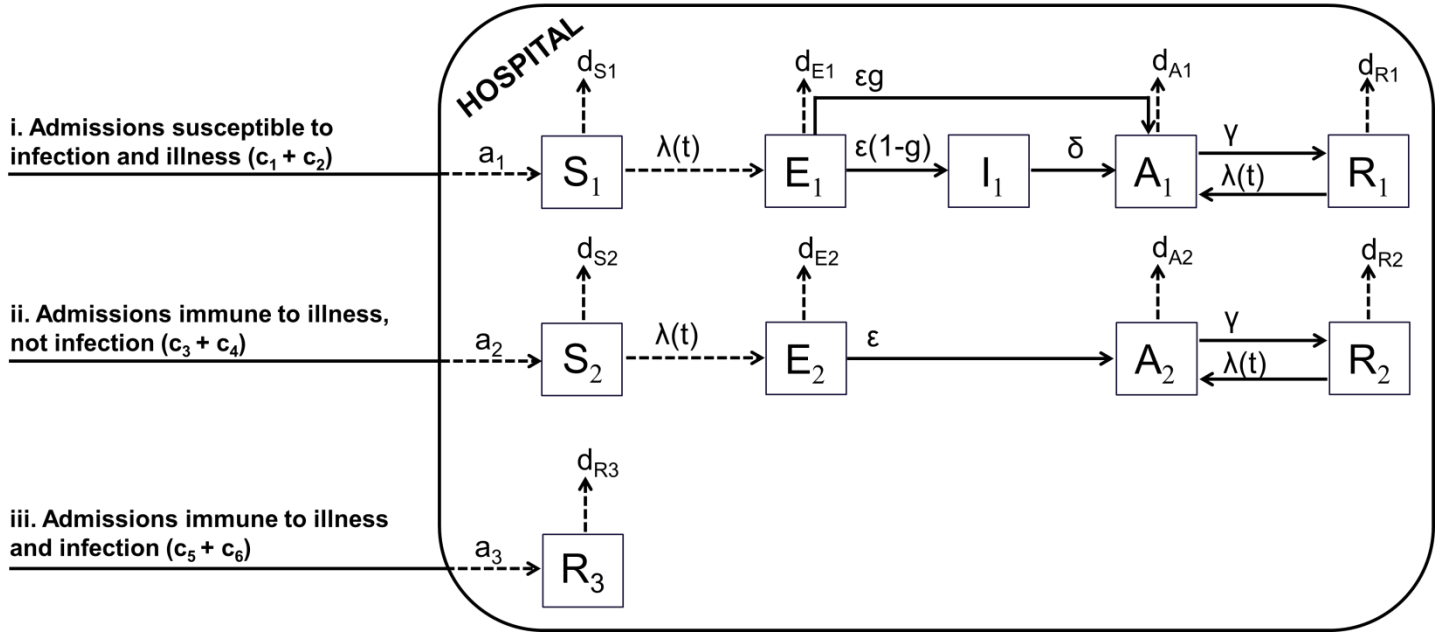
The hospital ward occupancy was then simulated for 365 days in total (see Appendix in section 5.8 for details). Next to the proposed benchmark occupancy levels of 85%, 90%, and 92%, we considered the level of full capacity as well as the additional trolley bed capacity.

5.4.1.3 Compartmental model of norovirus outbreaks

We nested a transmission-dynamic compartmental model within the hospital model to simulate norovirus outbreaks. We implemented a stochastic model using the Gillespie algorithm,^[292] which is based mathematically on Monte Carlo simulation of the time to the next event before determining which event occurs.^[293] The transmission model simulated an extended susceptible-infectious-recovered (SIR) process (Figure 31),^[293,294] with an additional exposed/latently infected compartment E , during which time patients incubate norovirus without symptoms but they are already 5% as infectious as a symptomatic case,^[79] and an asymptomatic infection compartment A , in which patients

are again only 5% as infectious as a symptomatic case.^[79] Inpatients immune to illness but not infection (admission group ii.) lacked the symptomatic compartment I , while inpatients immune to both illness and infections (admission group iii.) were captured in only a recovered/immune compartment, R_3 .

Figure 31. Compartmental model of norovirus outbreaks on hospital wards.



S_{1-2} : susceptible, E_{1-2} : infectious (latently/exposed), I_1 : infectious (symptomatic), A_{1-2} : infectious (asymptomatic), R_{1-3} : recovered/immune, a : admissions, d : discharges, $\lambda(t)$: force of infection, g : proportion asymptotically infected, ϵ : 1/incubation period, δ : 1/symptomatic period, γ : 1/asymptomatic period. c_1 – c_6 indicate the proportions of people in the community stratified by age and natural immunity to norovirus.

The equations of the compartmental model are as follows:

$$\begin{aligned}
 dS_1/dt &= a_1 \cdot N - (d_{S1} + \lambda(t)) \cdot S_1 \\
 dE_1/dt &= \lambda(t) \cdot S_1 - (d_{E1} + \epsilon) \cdot E_1 \\
 dI_1/dt &= \epsilon \cdot (1 - g) \cdot E_1 - \delta \cdot I_1 \\
 dA_1/dt &= \epsilon \cdot g \cdot E_1 + \delta \cdot I_1 + \lambda(t) \cdot R_1 - (d_{A1} + \gamma) \cdot A_1 \\
 dR_1/dt &= \gamma \cdot A_1 - (d_{R1} + \lambda(t)) \cdot R_1 \\
 \\
 dS_2/dt &= a_2 \cdot N - (d_{S2} + \lambda(t)) \cdot S_2
 \end{aligned}$$

$$\begin{aligned} dE_2/dt &= \lambda(t) \cdot S_2 - (d_{E2} + \varepsilon) \cdot E_2 \\ dA_2/dt &= \varepsilon \cdot E_2 + \lambda(t) \cdot R_2 - (d_{A2} + \gamma) \cdot A_2 \\ dR_2/dt &= \gamma \cdot A_2 - (d_{R2} + \lambda(t)) \cdot R_2 \end{aligned}$$

$$dR_3/dt = a_3 \cdot N - d_{R3} \cdot R_3$$

where:

S_{1-2} : susceptible inpatients

E_{1-2} : exposed (latently infected, infectious) inpatients

I_1 : symptomatic (infectious) inpatients

A_{1-2} : asymptomatic (infectious) inpatients

R_{1-3} : recovered (immune to illness) inpatients

N : $S_{1-2} + E_{1-2} + I_1 + A_{1-2} + R_{1-3}$, dependent on admission groups being occupied on day (t)

a_{1-3} : admission rates

d_{1-3} : discharge rates

$\lambda(t)$: force (rate) of infection

g : proportion asymptotically infected

ε : rate of 1/incubation period

δ : rate of 1/symptomatic period

γ : rate of 1/asymptomatic period

The probability that a susceptible inpatient becomes latently infected is determined by the force of infection, $\lambda(t)$. Latently infected patients may not develop symptoms, and recovered patients in compartments R_{1-2} may become asymptotically infected again while still in hospital at a rate identical to $\lambda(t)$.^[40,58,295] Inpatients in compartment R_3 are naturally immune to infection, which is why they cannot become asymptotically infected and do not contribute to sustained transmission.

We calculated $\lambda(t)$ according to the Reed-Frost equation,^[296] which accounts for the probability p of norovirus being transmitted when any given susceptible patient on the ward comes into contact with at least one infected patient on the ward,^[293] and we assumed a reduced infectiousness for the A and E compartments with a proportion of 0.05.^[79]

$$\lambda(t) = 1 - (1 - p)^{(0.05 \cdot E1(t) + I(t) + 0.05 \cdot A1(t) + 0.05 \cdot E2(t) + 0.05 \cdot A2(t))}, \text{ for } I > 0$$

Further, p was estimated based on the basic reproductive ratio, R_0 , the infectious period (i.e., incubation, symptomatic, and asymptomatic periods), and the proportion of susceptible patients on the ward (see Appendix in section 5.8):^[83,293]

$$p = R_0 / (\text{infectious period} \cdot \text{susceptible ward population})$$

R_0 is a metric indicating the number of secondary cases infected by an infectious individual in a completely susceptible population.^[293]

Inpatients were discharged at all stages during an outbreak at a defined rate, except for inpatients in the symptomatically infected compartment I , who were kept in the ward until they recovered. We counted infections as an outbreak when at least two inpatients became symptomatically infected,^[184,224,225] and we assumed that wards were closed for new admissions.^[87]

Once the outbreak model had reached its end, the ward model continued randomly admitting and discharging patients for the rest of the 365 days (cf. section 5.4.1.2), starting on the first day after the symptoms resolved in the last symptomatic patient involved in the outbreak model.

In order to explore the impact of norovirus outbreaks on hospital bed pressures, we investigated how often the simulated occupancy exceeded the occupancy level at the time of the outbreak (had there not been an outbreak); the full bed capacity of the ward; and the full capacity plus additional trolleys. For all three measures we assumed that the ward had been closed for new admissions after three days to reflect current practices.^[107]

5.4.1.4 Risk of norovirus infection in hospital

We used both models of the ward (section 5.4.1.2) and outbreaks (section 5.4.1.3) to determine the daily risk of an inpatient becoming infected with norovirus on a hospital ward: Within the ward model, there was the risk of one inpatient on the ward becoming infected with norovirus each day. This infection risk was evaluated each day with a uniform random draw that would set off the nested outbreak model if the number drawn was smaller than the value of the daily risk of infection. Not all infections, however, lead in reality to outbreaks (i.e., more than one case). Likewise, due to the stochasticity of the outbreak model (cf. section 5.4.1.3), it is possible for the infection to go extinct after infecting the index case, with no outbreak occurring even for values of the basic reproductive ratio, R_0 , greater than 1.0 (and, vice versa, outbreaks may occur by chance when $R_0 < 1.0$).^[293]

The (unknown) value of the infection risk was determined by fitting the annual outbreak incidence per ward to the mean incidence of 1.33 (95%-confidence interval, CI: 1.16-1.51) outbreaks per ward reported during an epidemiological surveillance study in England that observed 171 inpatient wards over one year.^[41] We assumed the outbreak incidence to be normally distributed, and the model fit was confirmed by visual inspection.

The infection risk was further modelled with a cosine function given that norovirus-associated infections occur more often during winters (see Appendix in section 5.8).^[285]

5.4.2 Model parameters

For an overview of parameters, see Table 33.

Table 33. Model input parameters, distributions and sources.

Parameter	Description	Value	Unit	Distribution	Sources
t_{max}	time horizon	365	days	Fixed	-
r_A	immune to illness, not infection	0.292	proportion	Beta(0.292; 0.5 ^a)	[102]
r_R	immune to illness and infection	0.375	proportion	Beta(0.375; 0.5 ^a)	[102]
c_e	elderly people in the community	0.180	proportion	Fixed	[297]
a_e	elderly inpatients in hospital	0.410	proportion	Fixed	[244]
a, d	admissions/discharges, based on the mean length of stay in England in 2015	1/5	rate	Poisson(0.2)	[244]
w	hospital ward bed capacity	19.75	per bed-day	Lognormal(19.75, 6.17)	[41]
w_T	additional trolley beds (rounded)	$0.1 \cdot w$	per bed-day	Dependent on w	c
o	bed-day occupancy	0.890	rate	cosine; see text	[291]
BD_U	beds kept empty for infection control, based on all beds occupied (BD_o)	0.2	number	Poisson($BD_o/(1-0.2)$ - BD_o)	[268]
ε	incubation period in days	1.0	rate ($1/\varepsilon$)	Gamma($\mu=1.0, \sigma=1.0$)	[58,75,295]
δ	symptomatic period in days	3.0	rate ($1/\delta$)	Gamma($\mu=3.0, \sigma=3.0$)	[40,58,295]
γ	asymptomatic period in days	2.0	rate ($1/\gamma$)	Gamma($\mu=2.0, \sigma=2.0$)	[58]
g	people infected asymptotically	0.292	proportion	Beta(0.292; 0.5 ^b)	[102]

a: 97.5th percentile; assumption

b: 99.999th percentile; assumption

c: assumption

5.4.2.1 Classification tree for the general community at risk of being admitted

Parameters for the natural immunity to norovirus were derived from the placebo group of the phase II randomised controlled trial (RCT) of a norovirus vaccine-candidate challenge study.^[102] We calculated the number of people not norovirus infected ($n=18$; 37.5%) to inform the proportion of immunity to infection (i.e., $C_5 + C_6$ in Figure 35), and the number of people that were norovirus infected but not ill ($n=14$; 29.2%) informed the proportion of immunity to illness (i.e., $C_3 + C_4$).

5.4.2.2 Hospital ward model

While individuals aged ≥ 65 years make up 18.0% of the population in England,^[297] they make up 41.0% of all hospital stays (see Appendix in section 5.8 for technical details).^[244] The random admission and discharge rates into the wards were informed by the mean national length of hospital stay of 5 days.^[244]

5.4.2.3 Compartmental model of norovirus outbreaks

Clinical and epidemiological input parameters describing norovirus outbreaks (cf. Figure 31) were obtained from peer-reviewed publications (see Table 33).^[40,58,75,102,295]

Values of R_0 for norovirus outbreaks in hospitals range between 1.6 and 4.3.^[83,279,298] Following the incubation period of 0.5-2 days,^[58,75,295] inpatients are symptomatic for 2-5 days,^[40,58,295] with a median 3 days reported for England.^[40] Afterwards, patients remain asymptotically infectious for at least 2 days after symptom resolution following the conventional contact precaution advice.^[58]

The number of patients in compartment I over time was used to calculate the bed-days occupied by norovirus patients. Bed-days lost unoccupied were approximated using their estimated proportion of 20% on all bed-days lost (occupied and unoccupied) due to norovirus in hospitals during winter in England (cf. Chapter 3).^[268]

We ran 1,000 simulations of the model. In order to account for parameter uncertainty, we ran the model probabilistically using Monte Carlo sampling from the input parameters from their prior distributions listed in Table 33.

All analyses were performed with R version 3.4.3 in RStudio,^[299] using the R-package *GillespieSSA* for the outbreak model.^[292]

5.5 RESULTS

5.5.1 Hospital ward model: Baseline without norovirus

In the baseline, the occupancy varied in the 1000 simulated typical hospital wards between a mean of 88.6% in the summer (April to September) and a mean of 91.5% in the winter (October to March; see Figure 32 for one example run of the simulation illustrating different levels of bed occupancy). The model indicates that the wards had bed occupancies above a level of 85% on 207 days a year (Table 34), while the full capacity was reached on 27.8% of the days (mean 101.4 days, range 34-206). The additional trolley bed capacity was exceeded on 13.5% of the days (mean 49.1 days, range 5-121).

Figure 32. Illustration of one simulation run of the ward model for a full capacity of 20 beds plus an additional 2 trolley beds in the hallway.

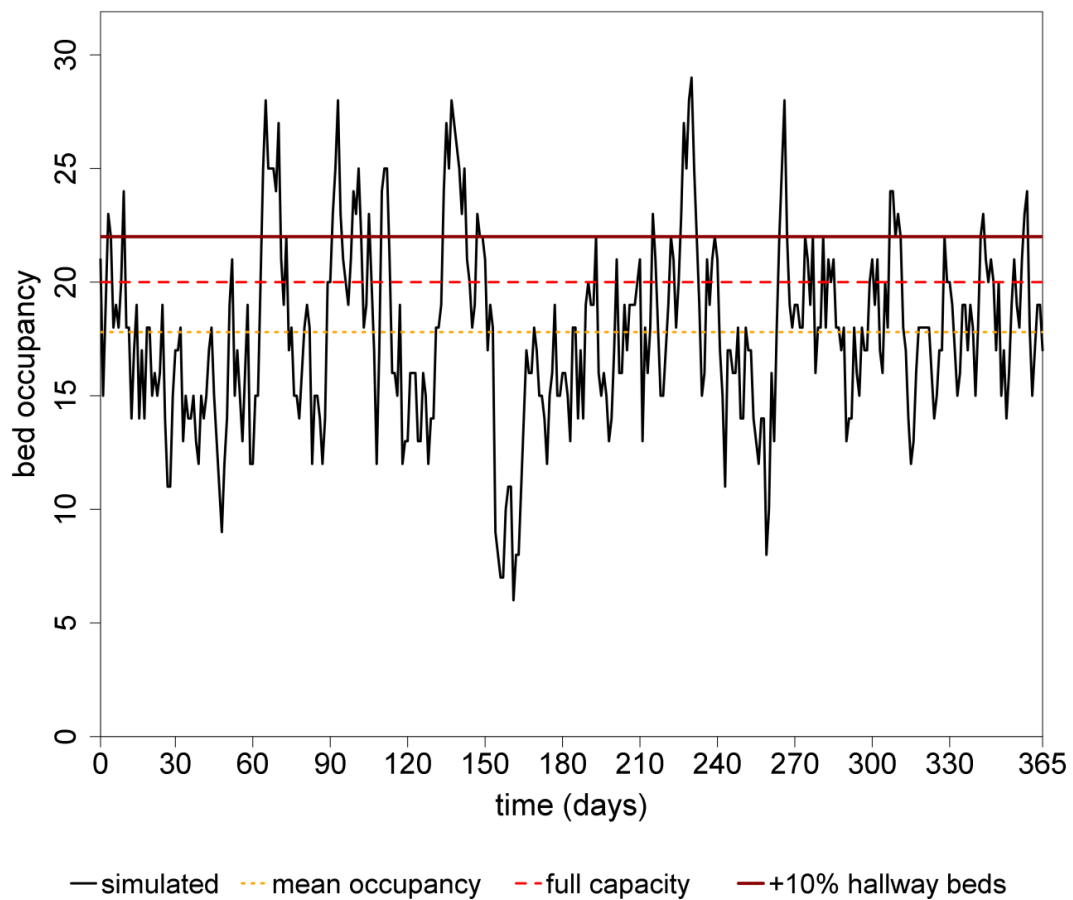


Table 34. Model results for different levels of bed occupancy.

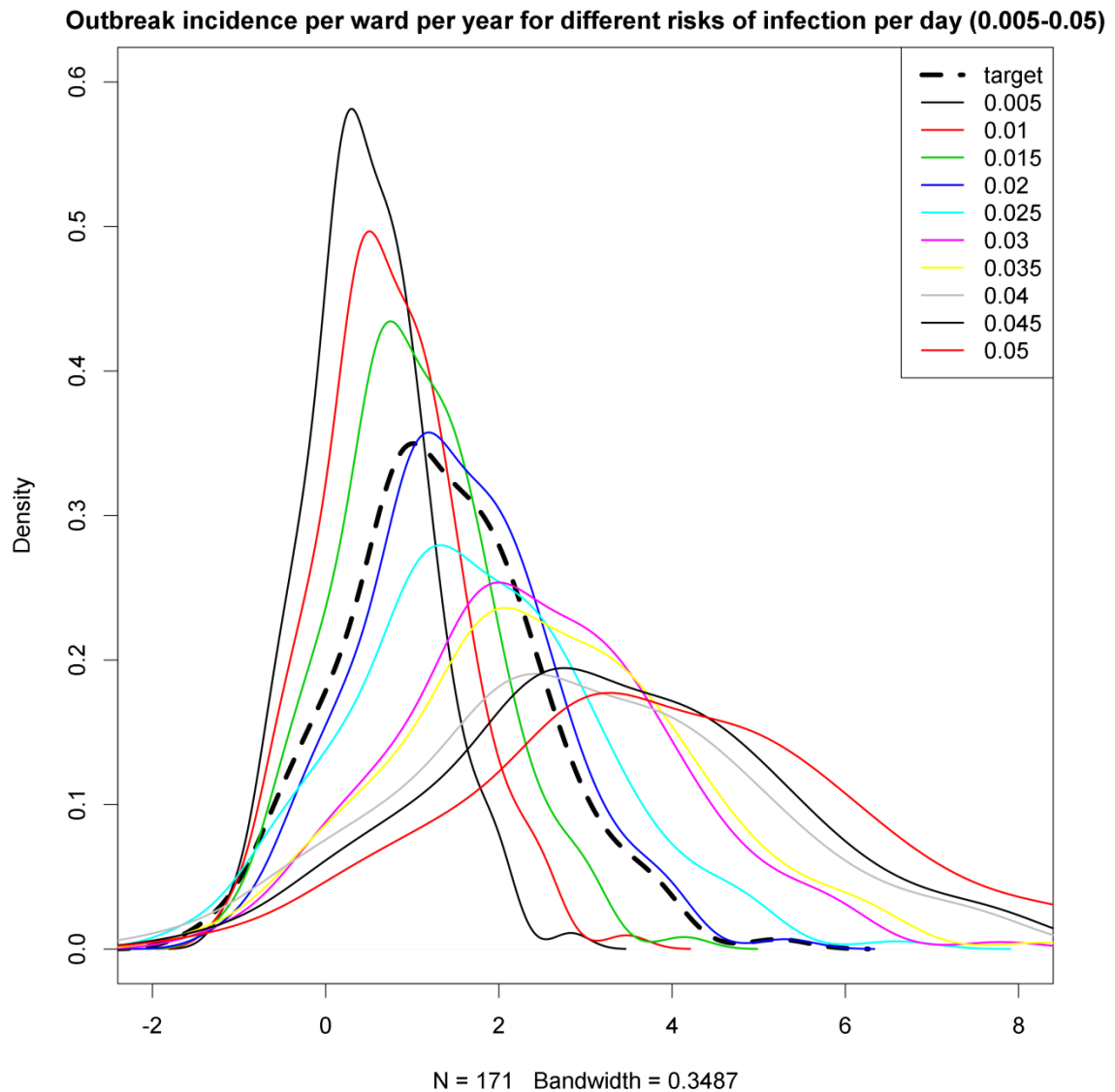
Description	Nr. of days occupancy reached specified level (%)	% of outbreaks where new admissions reached specified level (95%- CI)	Nr. of new admissions reaching specified level during outbreaks (range)
occupancy level at the start of the outbreak	n/a	83.0% (80.8–85.1%)	6.81 (0–44)
occupancy level: 85%	207.2 (56.8%)	72.9% (70.3–75.5%)	3.10 (0–17)
occupancy level: 90%	174.8 (47.9%)	67.6% (64.9–70.4%)	2.61 (0–16)
occupancy level: 92%	164.2 (45.0%)	65.3% (62.5–68.0%)	2.42 (0–14)
occupancy level: 100% (full capacity)	101.4 (27.8%)	46.7% (43.8–49.7%)	1.47 (0–12)
occupancy level: 110% (trolley beds)	49.1 (13.5%)	28.1% (25.4–30.8%)	0.72 (0–10)

CI: confidence interval

5.5.2 Norovirus outbreaks model

The daily risk of an inpatient becoming infected matched the annual incidence of 1.33 outbreaks per ward at a value for the infection risk of 0.02 (Figure 33). Using this value, the model predicted a mean incidence of 1.46 (95%-CI: 1.38-1.54) outbreaks on the hospital wards annually, resulting from an average of 6.24 (95%-CI: 6.09-6.40) infections per ward per year. There was a 76.9% chance of stochastic extinction after infection of an index case, i.e. without an outbreak occurring.

Figure 33. Different values for the daily risk of an inpatient becoming infected fitted to the annual outbreak incidence per ward.



The simulated outbreaks lasted for a mean of 8.33 days, with a mean of 2.60 symptomatic patients occupying 10.89 bed-days. Additionally, 2.67 bed-days were kept unoccupied for infection control. In total, a mean 13.56 bed-days were used for norovirus per outbreak, and occupancy levels increased by a mean of 8.1% (i.e., 1.6 longer staying inpatients).

When looking at the impact of outbreaks for alternative patients who wait for free beds to be admitted, the wards were closed to new admissions for a mean of 5.48 days during outbreaks. New admissions waiting for free beds occurred in 83.0% of outbreaks (Table 34), with a mean number of 6.8 new admissions (range 0—44) that waited for free

beds when closing the ward at the occupancy level of the start of the outbreak and assuming that new patients cannot be accommodated in the ward. This number of new admissions is equivalent to an additional demand of hospital beds of a mean 31.2%.

When assuming that new patients can be accommodated up to the full capacity of the ward, the full capacity was exceeded in 46.7% of outbreaks by a mean of 1.5 (range 0–12) new admissions waiting for free beds. This number of new admissions is equivalent to an additional demand of beds of 6.9%.

5.6 DISCUSSION

This study examined the dynamics of norovirus outbreaks in a typical English ward by fitting a dynamic transmission model to data on outbreak size, and accounting for the different immunity status in the population at risk of admission. Best fitting parameters were then used to simulate outbreaks in order to determine the impact of norovirus outbreaks on bed pressures.

5.6.1 Summary of key findings

We found that the daily risk of infection per ward and per year was approximately 2%. In the majority of simulations (76.9%), the model predicted that the infection would not spread beyond the index case and cause outbreaks.

In the baseline, the bed occupancy of the wards reached their full capacity on more than one-fourth of the days annually (27.8%). With norovirus, the situation worsens as it adds to the bed pressure in most outbreaks (83.0%). During outbreaks, occupancy levels were expected to increase by a mean of 8.1% from longer staying inpatients.

Even when assuming that wards can accommodate new admissions up to their full capacity and an additional 10% trolley bed capacity, new admissions will be forgone 28% of the time when outbreaks occur, with a mean number of 0.72 new admissions (which add to the bed pressures by an additional 3.3%, i.e., $0.72/(19.8 + 2)$).

5.6.2 Implications for policy and practice

This study showed the impact of norovirus outbreaks in hospital on bed occupancies, which rose to critically high levels that exceeded the full capacity in 46.7% of outbreaks, with a mean 1.5 (range 0—12) new admissions waiting for free beds.

Also, this study supports the findings of increased bed occupancies leading to bed shortages and periodic crisis. Hospital bed occupancy levels in England are high already without outbreaks, and it is uncertain that the recently proposed benchmark levels of bed occupancy between 90% and 92% by various public bodies in England are feasible in practice at current levels of bed capacity and demand for hospital care in England.

Considering the recurring bed pressures faced by NHS hospitals in England, which are in part due to norovirus,^[268] reducing illness and outbreaks will increase capacity that can be used for other patients. In England, these outbreaks involve more than 11,000 infected patients and almost 3,000 infected staff annually,^[71,285] while the total number of all norovirus-infected inpatients may be above 100,000 and incur financial expenditures to the NHS in England of £108 million annually.^[285] The opportunity costs of the bed-days used for norovirus have been estimated with between £190 million and £298 million annually – roughly 2-3 times higher than the financial expenditures.^[285] This does not include any opportunity costs for bed-days blocked for other reasons than norovirus, which may also arise as our study suggests but did not quantify.

5.6.3 Strengths and limitations

The stochastic model presented here followed hospital wards in England over one year, and simulated norovirus outbreaks using a nested transmission-dynamic model. The model carefully considered the characteristics of sustained transmission of norovirus during outbreaks and the different levels of natural immunity in the population, as well as the features of typical hospital wards in England.

Previous studies modelling norovirus in hospital mainly looked at the impact of ward closure for a single hospital or within a region,^[83,108,298] as well as other infection control and contact precaution measures.^[279,300] Similar to these studies, we assumed homogeneous mixing of patients on the ward. During outbreaks, we assumed that the ward was always closed for all but the first 3 days of the entire outbreak duration. This is consistent with a recent estimation as well as the fact that over 95% of outbreaks lead to

ward or bay closures.^[71,107] However, we did not consider overspill into other wards, and in reality cases may be transferred into another ward or hospital, which may impact extended transmission and could make a series of connected cases look like separate outbreaks. Moreover, the simple stochastic model of admissions and discharges is not realistically capturing all the drivers of hospital bed use throughout the year, which are driven by a multitude of factors (e.g. dynamic changes to capacity, other seasonal infections, bad weather, or staffing levels).

We informed the proportion of immunity to infection from the number of people not norovirus infected in the RCT challenge study,^[102] assuming that anyone not infected after norovirus challenge must be immune. The derived value of 37.5%, however, is consistent with previously published estimates of one-third and up to 50% of a population.^[79]

In this study we considered the full capacity level at 100% and an additional 10% trolley bed capacity, which results in a capacity above 100%. Obviously, very high levels of occupancy cannot be maintained for longer than a few days; trolley beds in the hallway can only be temporary when trying to accommodate peaks in the demand for hospital beds. Moreover, occupancy levels vary per specialty and ward, which we did not capture here by using the national average of all acute care hospitals. Lastly, our study did not look at adverse effects for patients and the care that they receive when admitted, or intangible effects like the stress and anxiety level for both patients and staff. Both are likely to rise with higher occupancy levels.

The period of one year was chosen to reflect the short duration of infection in most cases.^[58,295] Although it was previously thought that immunity may only last for 0.5-2 years, recent modelling work has shown that immunity may wane only after 5-8 years.^[79] However, recovered patients becoming fully susceptible again were not explicitly considered in this study, only implicitly by keeping proportions constant. Likewise, infections among healthcare staff were not modelled in the compartmental model due to the lack of suitable data. A modelling study for Dutch hospitals showed that symptomatic patients instead of asymptomatic healthcare workers are the drivers of NoV transmission.^[58,301]

Lastly, with the phase III RCT of the norovirus vaccine-candidate expected to be published soon, robust data will become available to model a vaccination uptake

programme.^[56] The model used for the study here could then be extended to evaluate the impact of vaccination (i.e., vaccine-induced immunity), which may not be conferred to all subjects receiving the vaccine as indicated by early results of the phase II challenge study.^[102]

5.7 CONCLUSIONS

This study found that norovirus outbreaks add to existing bed pressures and impact new admissions of patients waiting for a free bed. In addition, recently proposed bed occupancy levels between 90% and 92% may not be feasible in practice at current levels of capacity and demand for hospital care. Current hospital financing and planning may need to be revised.

Future research needs to consider the direct implications on health outcomes (e.g. the increased risks of in-hospital mortality and hospital-acquired infections). In order to reduce the hospital burden of norovirus, it will be important to evaluate the cost-effectiveness of norovirus vaccination once robust data have become available.

5.8 SUPPLEMENTARY MATERIAL

We used the following set of equations to separate people in the community according to the natural or vaccine-induced immunity against norovirus infection and/or illness, and by age (cf. Figure 30).

$$c_1 = (1 - r_A - r_R) \cdot (1 - c_e)$$

$$c_2 = (1 - r_A - r_R) \cdot c_e$$

$$c_3 = r_A \cdot (1 - c_e)$$

$$c_4 = r_A \cdot c_e$$

$$c_5 = r_R \cdot (1 - c_e)$$

$$c_6 = r_R \cdot c_e$$

where:

c_e : proportion of elderly people aged ≥ 65 years in the community

r_A : proportion recovered/immune to illness but not infection (asymptomatic)

r_R : proportion recovered/immune to illness and infection

For typical hospital wards in England, we modelled the bed capacity drawn from a normal random variable based on a sample of 171 inpatient wards in England with a median capacity of 20 beds (range 1-38).^[41] Given the large number of 171 wards, we estimated the mean and standard deviation from the median and range following a previously published approach.^[302]

$$\begin{aligned} \mu &= (1 + 2 \cdot 20 + 38) / 4 \\ sd &= (38 - 1) / 6 \end{aligned}$$

The inpatient population occupying beds in the hospital ward was initialised accordingly for $t = 0$, ensuring a higher proportion of the elderly for the hospital occupancy, h , to reflect national hospital statistics^[244] based on the proportions c as follows:

$$h_k = \begin{cases} w \cdot o(t) \cdot a \cdot (1 - a_e) \cdot \frac{c_k}{(1 - c_e)}, & k \in \{1,3,5\} \\ w \cdot o(t) \cdot a \cdot a_e \cdot \frac{c_k}{c_e}, & k \in \{2,4,6\} \end{cases}$$

where:

w : bed-day capacity of the hospital ward

$o(t)$: daily hospital bed occupancy rate

a : mean hospital admission rate

a_e : proportion of inpatients aged ≥ 65 years

c_k : proportion k of people in the community

c_e : proportion of people aged ≥ 65 years in the community

When initialising the occupancy on day $t = 0$, $o(t)$ is set equal to the annual mean bed occupancy rate in hospital, and a is set to 1. For each day afterwards, people in need of hospitalisation were randomly admitted from the community into the admission groups using a Poisson distribution to allow for variability in patient arrival. The admission rate a was set equal to $1/\text{LOS}$, where LOS is the mean length of stay in hospital.^[244] The mean occupancy rate o was adjusted for seasonality with a cosine function fitted to the quarterly occupancy data of all hospital bed-days in England in 2015.^[291]

$$o(t) = o + o \cdot 0.023 \cdot \cos(2 \cdot \pi \cdot t / t_{max})$$

Each day, inpatients may leave the ward according to a Poisson distribution, too, conditional on the number of patients in each of the three groups on the previous day ($t-1$). The daily sum of discharged patients is then equal to:

$$\sum_{k=1}^3 \begin{cases} a_k(t-1) \cdot d & \text{if } 1 \leq t < 366 \\ 0 & \text{otherwise} \end{cases}$$

where:

d : mean discharge rate

t : daily steps of the hospital model

The daily risk of an infection event was modelled with a cosine function, too, which was fitted to the expected norovirus-associated infection events in hospital in England in 2015^[285].

$$y(t) = y + y \cdot 0.7 \cdot \cos(1.6 \cdot \pi \cdot t / t_{max})$$

where:

$y(t)$: daily risk of an infection event in hospital

For the Reed-Frost equation, we calculated p (which is equivalent here to the rate of transmission, β)^[293] as follows:

$$p = R_0 / ((\varepsilon + \delta + \gamma) \cdot (w \cdot (1 - r_R) \cdot o))$$

where:

R_0 : basic reproductive ratio

ε : incubation period

δ : symptomatic period

γ : asymptomatic period

w : bed-day capacity of the hospital ward

r_R : proportion recovered/immune to illness and infection

o : mean hospital bed occupancy rate

5.8.1 Other mathematical modelling studies for norovirus

At least fourteen modelling studies of norovirus have been published as of November 2017,^[303] which have considered a range of different methods, populations, interventions, settings and outcomes. The most relevant studies for this thesis are those that looked at norovirus outbreaks in healthcare settings, specifically hospitals:

1. Vanderpas and colleagues (2009) used a deterministic transmission dynamic susceptible-exposed-infectious-recovered (SEIR) compartmental model to investigate a norovirus outbreak on four wards in a long-term care facility adjacent to a hospital in Belgium in December 2007, and the impact of ward closure to new admissions.^[298] The model assumed homogeneous mixing of all patients. It did not consider natural immunity, loss of immunity (i.e., movement from the recovered to the susceptible compartment), mortality, or asymptomatic infection. Patients were admitted into the susceptible compartment at a rate inverse to the mean length of stay, and were discharged from each other compartment at a rate equal to the admission rate. Results indicated that high turn-over rates (i.e., short lengths of stay of ≤ 2 days) produced the highest number of cases, which declined exponentially as turn-over rates decreased. The authors therefore concluded that closing wards to new admissions may be beneficial to reduce the number of cases by decreasing the turn-over rate and prolonging the length of stays.^[298]
2. Lee and colleagues (2011a) compared an unmitigated norovirus outbreak in a hospital ward with the separate implementation of various infection prevention and control strategies, including increased hand hygiene, enhanced use of contact precautions, increased disinfection of the ward, staff exclusion policies, patient isolation (with up to four empty beds), or ward closure (with up to five empty beds).^[202] For each intervention, the authors used a stochastic decision-tree model of 1 million runs and one primary case infecting one generation of secondary cases based on a low R_0 of 3.74 (95%-CI: 3.179–4.301) or a high R_0 of 7.26 (95%-CI: 5.26–9.25), which they obtained from the outbreaks reported by Vanderpas et al.^[298] and Heijne et al.^[304], respectively. The intervention efficacy reduced R_0 correspondingly, i.e. $R_0 \cdot (1 - \text{efficacy})$. In sensitivity analyses, the number of initial cases and R_0 were varied, as well as the intervention efficacy and the room size, ward size, and occupancy of the ward. The perspective was that of the hospital and the outcome the cost savings achieved with the different interventions. Infectious patients had a probability of becoming symptomatic of 66.3%, leading to an excess length of stay equivalent to a mean 2 days (95%-CI: 0.96–13.05 days) based on other publications. The model assumed no natural or acquired immunity, and homogeneous mixing of patients within the ward. Results indicated that most measures were cost-saving at all levels of effectiveness except for the patient isolation and ward closure, which were only cost-saving at an efficacy of at least 50% and when a maximum of only one bed became unavailable for infection control.^[202]

3. Lee and colleagues (2011b) used a stochastic transmission dynamic susceptible-exposed-infectious-recovered (SEIR) compartmental model to evaluate the economic impact of norovirus outbreaks for different ward sizes and outbreak durations.^[279] The perspective was that of the hospital and the outcome the revenue losses associated with bed-days lost as they were occupied by symptomatic patients. Patients in the infectious compartment could become symptomatic at a probability of 66.3%, leading to an excess length of stay equivalent to the symptom duration. Patients also stayed protected for the remainder of the duration of the study due to the relatively short durations of outbreaks of about 20 days. The model assumed no pre-existing natural immunity of patients on the ward and homogeneous mixing of patients within the ward. Results indicated that the ward size and the number of cases were the most influential cost drivers of the study.^[279]
4. Bartsch and colleagues (2014) investigated the spread of norovirus outbreaks due to patient transfers among different healthcare facilities in one region of the USA, and the impact of contact precautions.^[83] They modelled transmission within each general ward and intensive care unit of the 29 acute care hospitals in Orange County, California, in 2008. The authors used an agent-based simulation model with the four states “susceptible”, “exposed”, “infectious”, and “recovered”. They ran the model 100,000 times for 5 years and with daily transition probabilities. The model assumed homogeneous mixing of patients within the two types of wards, and allowed for transfers from intensive care wards to general wards. The individual infection risk (λ) was modelled with the Reed-Frost formula, which takes into account the probability (p) of coming into contact with at least one of the infected individuals (I) at time t : $\lambda_t = 1 - (1 - p)^{I_t}$.⁷ Infectious patients experienced symptoms with a probability of 66.3% and could not be discharged. Only asymptotically infected patient could spread the virus, for whom infectiousness was assumed to be reduced by 50%. Moreover, the recovered state was assumed to confer protection against symptoms but not infection; these patients could thus become asymptotically infected again. They also investigated in the impact of using contact precautions (i.e., gloves and gowns) with an assumed effectiveness of 50–60%. In the base case the authors assumed no pre-existing natural immunity of patients, while in a scenario analysis they explored 27% of patients being protected by natural immunity and thus starting in the recovered state. However, the model did not include the impact of ward closures to new admissions and restrictions on patient transfers, or any mortality. Overall, the ongoing sequential outbreak among the hospitals never exceeded 5.5 months, with most transmission occurring within 2–4 weeks after the initial outbreak. Contact precautions reduced the number of norovirus cases and the probability of

⁷ The formula is used so that the infection risk is not overestimated as it would be using the conventional calculation of $\lambda_t = \beta I_t$, where β is the effective contact rate.^[293]

outbreaks spreading to other hospitals, but not the number of hospitals with norovirus cases.^[83]

5. Sadique and colleagues (2016) evaluated the cost-effectiveness of hospital ward closures during norovirus outbreaks. They modelled outbreaks in admission, general medical, and long-stay wards for 14 hospitals in England.^[108] They ran 100,000 stochastic simulations of a decision-tree-like transmission model for 1 year each to compare different timings of closure (none, day 1, 3 or 5 after initial infection) and effectiveness of reduced between-ward infectiousness (by 0%, 25%, or 50%). Daily time steps were used and the number of newly infected wards determined from a negative binomial distribution. The end of an outbreak was determined by daily probabilities from a previous epidemiological study^[41] but not exceeding three weeks. Outcomes included the incremental cost per case and per outbreak avoided. The perspective was that of the hospital, and they calculated unoccupied bed-days lost by multiplying the duration of closure with a mean 3.6 bed-days lost for each day based on a previous epidemiological study.^[41] Similarly, staff absence costs were calculated by multiplying the mean length of staff absence with the unit cost of a nurse. Results indicated that ward closures were costly but able to reduce the number of outbreaks and cases by up to 55%, with incremental costs ranging from £10,000–£306,000 per outbreak averted and £500–£61,000 per case averted.^[108]

The study presented in this chapter adds to the literature by focussing on hospital outbreaks of norovirus and the additional bed pressure arising from these outbreaks when occupancy levels are already high at baseline (without norovirus). Insights into bed occupancy are specific to the periodic bed pressure situation of the NHS in England.

6 DISCUSSION AND CONCLUSIONS

“If among a nation of hunters, for example, it usually costs twice the labour to kill a beaver which it does to kill a deer, one beaver should naturally exchange for or be worth two deer. It is natural that what is usually the produce of two days’ or two hours’ labour, should be worth double of what is usually the produce of one day’s or one hour’s labour.”

Adam Smith, *The Wealth of Nations*, 1776.^[17]

This final chapter 6 discusses the main aims and ideas of the thesis, and places its content into a broader context. I reflect on the strengths and limitations of the novel approach, and its practical application to norovirus, and I provide recommendations for future policy making. The thesis is concluded by highlighting implications for research and practice.

The current costing convention in (health) economics uses market prices and financial expenditures as proxies for the value of the opportunity costs of resources. The main assumption behind this conventional approach is that “[...] costs of production are measured in money, and these reflect the value of output that *might have been produced* if the same resource inputs had been rationally applied in alternative employments.”^[5: p.11] This assumption hence only holds when the value of the inputs equals the value of the outputs, i.e. in perfectly competitive markets.

Owing to market imperfections in healthcare, resources like bed-days are unlikely to reach the equilibrium price, and thus their actual price or expenditure will most likely not converge to opportunity costs. Consequently, the need arises for considering the net benefit, and finding the optimal option and its second-best alternative.

For situations not requiring a monetary value, the displaced alternative could simply be determined as in the historic example of Adam Smith for the nation of hunters (see quote above).^[17] Looking at healthcare, one may be tempted to replace the animals with patients: “If *in the healthcare sector* it usually costs twice the labour to *treat a patient of*

type A which it costs to *treat* a *patient of type B*, one *patient of type A* should naturally exchange for or be worth two *patients of type B*.” The assumptions are still the same: Patients of type B are the second-best alternative forgone to patients of type A as determined by an agent’s objective of e.g. health maximisation, and the highest valued option does not lie outside the healthcare sector.

Nonetheless, most situations are beyond natural units of resources (like bed-days) and require a monetary exchange value. This complicates matters, especially in healthcare. For practical reasons, considering market prices and financial expenditures has become a widespread standard of costing despite its shortcomings, which is why it was already noted before that “[...] it has often been remarked that health economists recognize that market imperfections exist in health care, unless they are undertaking an economic evaluation”.^[4: p.58] It is against this background that this thesis needs to be read, which has aimed to propose an approach for addressing the existing shortcomings.

6.1 SUMMARY OF THE KEY FINDINGS

6.1.1 How to estimate the value of bed-days

In order to find out how to estimate the value of bed-days during epidemic and disease outbreaks in hospital (cf. research question 1 in section 1.4), chapter 2 started by tracing the existing methodologies of estimating the opportunity costs of resources that were developed over the last three centuries. In total, four different methodologies were identified, which showed that broad consensus exists in theory that opportunity costs represent the value of a resource in terms of its most valuable⁸ alternative use forgone (section 2.5.1).

The resulting taxonomic framework was then used to categorise nine approaches for bed-days that were found in a scoping literature review of the (health) economic and medical fields (section 2.5.2). For pragmatic reasons, the conventional approach of taking

⁸ The “most valuable forgone alternative” corresponds ideally to the second-best option, assuming that the optimal option is chosen. Otherwise when choosing a sub-optimal alternative, the net value of the optimal option needs to be added to the value of the chosen option to account for the forgone benefits.^[5]

market prices and accounting expenditures and assuming that they approximate to opportunity costs has been widely followed for bed-days. However, this assumption is only valid for the perfectly competitive market model, with waiting lists and other market imperfections disproving this model for the healthcare market. Therefore, the true value for the second-best use of bed-days likely differs from the value calculated using conventions, and very noticeably so during nosocomial outbreaks of infectious diseases due to the impact on supply and demand of hospital beds.

Nonetheless, some studies used the adequate approach of estimating net benefits for the perspective of providers aiming to maximise net revenues (sections 2.5.2.2 and 2.5.4). For decision makers aiming to maximise population health, no adequate approach was found that captures the (health) opportunity costs of hospital beds for displaced admissions (section 2.5.4).

Therefore, I have developed a novel approach in this thesis that builds on the idea of the net monetary benefit^[139,140] of the second-best patients forgone (section 2.5.5), which aims to overcome the previously identified issues of conventional approaches not capturing the health impact for displaced patients.

6.1.2 Costing the winter bed pressure due to acute gastroenteritis

Chapter 3 (and chapter 4) were used to estimate the hospital burden of norovirus in England, based on the most prominent costing approaches identified previously in chapter 2 (cf. research question 2 in section 1.4). In chapter 3, I turned to illustrating the conventional method of estimating costs for hospital bed-days using norovirus-associated gastroenteritis as case study. The dataset used operational data of hospital beds kept unoccupied for infection control during six winters across seven years, which is the time of increased demand for acute hospital care in England that results in periodic bed pressures. One of the main advantages of this dataset is that the number of bed-days are reported compulsorily by each acute care hospital, which is why only a small fraction of the data (0.34%) was miscoded or suspected to contain errors (see sections 3.4.1 and 3.6.2). Thus, the compulsory nature of the reports allows for a comprehensive overview of the impact of acute gastroenteritis on bed-days lost nationwide in winter.

Furthermore, this study is the first time that the issue of the missing values in the dataset has been addressed by imputing non-randomly missing values at provider-level, and

taking the lowest and highest value imputed as best and worst case estimates (section 3.4.2). Moreover, observations were filtered to a common range of dates recorded in all six winters to enable a fair comparison. An additional analysis was carried out for winter 2016/2017 as it tracked information for each day (i.e., the data collection did no longer contain missing values for weekends or public/bank holidays), which pointed to the actual value being between the best-to-worse case estimates (section 3.9.6).

This study is also the first attempt to identify outbreaks in the data. Whether the infectious gastroenteritis outbreak duration could be traced by following conventional definitions for outbreaks of norovirus was explored (i.e., more than one symptomatic case for more than one day, with symptom onset of cases within ± 48 hours; see section 3.4.3).^[184,224,225] The estimated duration of infectious gastroenteritis outbreaks was within the range of previously published studies.^[174,175,204]

Results indicated that bed closures due to diarrhoea and vomiting are a widespread issue among acute care hospitals in England, with a mean of 80% of hospitals being impacted each winter (section 3.5.1). Although only about 1.1–1.3% of the general and acute care beds available in England each day were closed due to diarrhoea and vomiting each winter, the median number of beds closed for each entire winter is equivalent to the entire median total bed capacity in England per day (section 3.5.1).

In addition, 20% of bed-days are lost unoccupied, which indicate opportunity costs for both the hospital (in terms of revenue losses) as well as society (in terms of potential health losses as no additional patients can be treated in the unused beds). The financial burden amounted to £6–£8 million per winter for the unoccupied bed-days only (section 3.5.3), which increased to £29–£37 million when considering all occupied and unoccupied beds (section 3.6). Arguably, the occupied beds do not represent a financial revenue loss for hospitals, but these beds are blocked for alternative patients and opportunity costs may arise from the lost opportunity to treat the patient who would have been admitted if the bed was available. The dataset did not allow determining how many beds were actually lost due to norovirus (cf. time-dependent bias), which has therefore been estimated in chapter 4. Once the number of bed-days is known, it is possible to use the new approach for quantifying the opportunity costs of bed-days (cf. chapter 2).

6.1.3 Financial expenditures vs. opportunity costs: hospital burden of norovirus

Chapter 4 provided a more comprehensive overview of the annual hospital burden of norovirus in England in order to demonstrate the difference between costing approaches. This study is first to combine individual-level norovirus outbreak data with national hospital surveillance and statistics to apply the novel approach for estimating the opportunity costs of bed-days from patients who cannot be admitted due to beds being unavailable. To this end, the study accounted for time-dependent biases, under-recording of norovirus in national databases of infection surveillance and hospital statistics as well as the potential impact of the vaccine introduced against rotavirus-associated gastroenteritis in July 2013.

Much of the complexity of this study arose due to the features of norovirus and the diverse surveillance systems and data sources in England (cf. section 4.4.1), with each of them having different objectives, which needed full interrogation to ensure they were used robustly (section 4.10). In particular, the study used the best available data sources for norovirus. Multivariate linear regression analysis was used to attribute the number of inpatient cases with gastrointestinal symptoms (and the bed-days occupied by them) to norovirus using the national hospital episode statistics database and laboratory surveillance count data at Public Health England (section 4.4.2.1). Given the large sizes of the data used for the regression analysis a linear model was chosen, but results were robust to a negative binomial model (section 4.10.2). The bed-days used by cases with a secondary diagnosis of norovirus-associated gastroenteritis were estimated more accurately than when using matched-cohort studies, which have shown to lead to overestimations. Instead, the excess length of hospital stays due to norovirus was estimated using a multi-state model and individual-patient data from a local hospital outbreak of norovirus (section 4.4.2.2). For the number of members of staff absent due to illness, as well as the number of bed-days lost unoccupied for infection control, the national surveillance data were not used directly but adjusted due to the known issue of under-reporting of outbreaks, cases and bed-days (section 4.4.2.3).

The results showed that norovirus is now the second-largest contributor of the gastrointestinal hospital burden (section 4.5.2.1). Also, the estimated median number of occupied and unoccupied bed-days that are used for norovirus per year is equivalent to

the entire daily NHS hospital bed capacity in England being unavailable for more than two days annually (section 4.6.1).

Chapter 4 also confirmed that the number of bed-days lost due to diarrhoea and vomiting (D&V) in winter (cf. chapter 3), which NHS England calls “number of beds unavailable due to D&V/norovirus like symptoms”, are indeed closely associated with norovirus as indicated by the linear regression analysis (section 4.10.4). The adjusted R^2 is suggestive of norovirus explaining more than 93% of the variation observed. Similarly, the same regression methodology was used to explore whether the bed-days recorded in HNORS were associated with norovirus due to the fact that the source of outbreaks may be of suspected or confirmed norovirus, with only between 60–70% being laboratory confirmed.^[71] The adjusted R^2 is suggestive of norovirus being able to explain more than 80% of the bed-days lost (cf. section 4.10.4).

Thus, although keeping bed-days unoccupied for infection control is an important contact precaution measure in clinical practice, this analysis showed that empty beds make a small contribution to the total economic burden of norovirus. The unoccupied beds make up only 10% of the total bed-days lost to norovirus (sections 4.5.2.4 and 4.10.8). This finding may be surprising to some, which is why extensive detail was provided on how the number of bed-days lost unoccupied was obtained (section 4.10.4). However, the study used the best available data, and the proportion of empty beds is thus unlikely to change to a great extent, even considering the uncertainties around it.

Lastly, as part of the new approach of valuing opportunity costs it became necessary to estimate the mean QALYs gained from hospital admissions (section 4.10.7), and thus enabling estimation of QALYs lost in prevented admissions. Mean age- and sex-specific health utilities were mapped for diseased individuals to the primary admission code,^[282] and patients were stratified into three sub-groups of a) acute life-threatening conditions, b) chronic conditions, or c) none of these conditions (section 4.10.7). Based on the remaining age- and sex-specific life expectancy from the Office for National Statistics in England (for patients in group a and b),^[284] a gradual decline of health was modelled over time, similar to previous studies using more sophisticated regression analyses.^[282,305] It was assumed here that (a) patients with acute life-threatening conditions survive with hospital treatment for their remaining age- and sex-specific life expectancy; (b) patients with chronic conditions maintain their health at a higher level with hospital treatment; and (c) patients with none of these conditions recover faster with hospital treatment but

there is no attributable effect of this hospital stay for the remaining life expectancy. Overall, the alternative patients forgone were estimated to have the potential to gain twice as many QALYs from hospitalisation as the norovirus patients who displaced them (sections 4.5.1 and 4.10.8).

Overall, valuing the burden of norovirus conventionally resulted in financial expenditures of £107.6 million annually for the NHS (section 4.5.3.1), while accounting for the opportunity costs from forgone patients with the novel approach resulted in £190–£298 million at a monetary value of £20,000/QALY, and a loss of 6,300 QALYs annually (sections 4.5.3.2 and 4.10.8). These results indicate that opportunity costs for treating norovirus in hospital are high, and the true cost may be roughly 2–3 times higher than the value calculated with conventional techniques.

6.1.4 Norovirus outbreaks in hospital and the additional impact on bed pressures

Finally, chapter 5 explored the transmission of norovirus during hospital outbreaks, and the additional impact on the bed occupancy level in acute care wards of the NHS in England (cf. research question 3 in section 1.4). The study used a model that stratified individuals in the general community at risk of being admitted by age to reflect the higher risk of hospitalisation for the elderly in England, and it also accounted for individuals being susceptible to norovirus infection and/or illness (section 5.4.1.1).

For the baseline situation of typical hospital ward occupancy levels without norovirus, a sample of 171 inpatient units in England and the national bed occupancy rate of all acute care hospitals in 2015 were considered for simulating random admissions and discharges (section 5.4.1.2). In order to explore the additional impact of norovirus outbreaks on the bed occupancy, a transmission dynamic mathematical model was built that simulated norovirus transmission within the ward. The model reflected the immunity of individuals to norovirus infection and/or illness as well as the asymptomatic transmission of norovirus before and after gastrointestinal symptoms appear (section 5.4.1.3). It was also assumed that conventional infection control and contact precaution measures were in place in that the wards were closed to new admissions after three days and patients were discharged at all times unless they were acutely symptomatic. The resulting bed pressure was then measured from longer staying inpatients as well as new patients awaiting admission to a free bed as compared to different levels of bed occupancy.

The model was also used to determine the daily risk of an inpatient becoming infected with norovirus on a hospital ward per year, and stochastic extinction after norovirus infected the index case, i.e. without an outbreak occurring (section 5.4.1.4). The model estimated that the daily risk of one inpatient becoming infected was 0.02 per ward per year (section 5.5.2), and a 76.9% chance of stochastic extinction (section 5.5.2).

Results also indicated that already in the baseline without norovirus the bed occupancies reached the full capacity of the wards on days that add up to more than three months each year, and even the additional 10% trolley bed capacity is regularly exceeded on days equivalent to more than 1.5 months (see section 5.5.1). With norovirus, the situation worsens rapidly as occupancy levels increased from longer staying inpatients by a mean of 8.1% during outbreaks (section 5.5.2).

Additional bed pressure from new patients awaiting admission arose in most outbreaks (83.0%), with a mean number of 6.8 new admissions forgone when closing the wards at the prevailing occupancy rate of the outbreaks (section 5.5.2). Even when assuming that these patients can be accommodated up to the level of full capacity of the ward and an additional 10% trolley bed capacity, a mean of 0.7 new admissions were forgone in 28% of the outbreaks, which is equivalent to an additional demand of beds of 3.3% (section 5.5.1). Consequently, despite hospital wards exhibiting some undeniable compensatory abilities to accommodate temporary supply and demand shocks, it seems reasonable to assume that opportunity costs occurred and may not even be avoidable in England given the high occupancy rates.

6.2 IMPLICATIONS AND RECOMMENDATIONS FOR POLICY AND PRACTICE

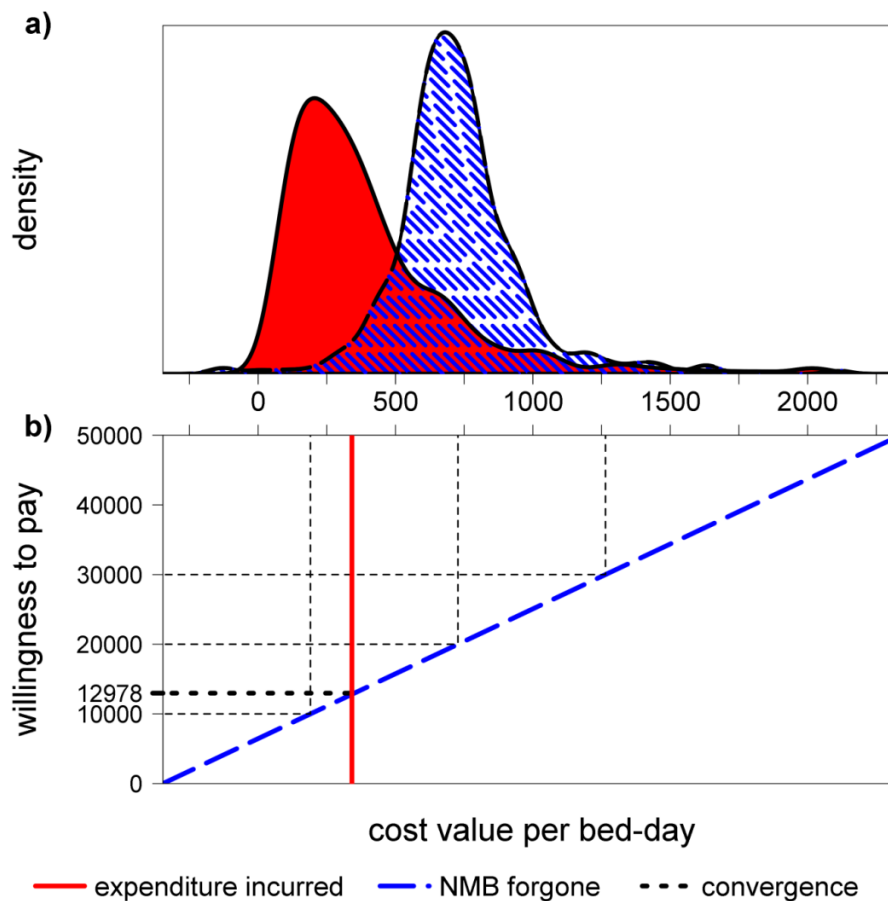
In order to guide reimbursement decision-making, policy makers and researchers in developed countries have been increasingly relying on health technology assessments (HTA), particularly on health economic evaluations.^[306,307] These evaluations require adequate cost estimates by considering the opportunity costs of resources.^[4]

Current costing conventions for opportunity costs, however, may be too simplistic in their assumptions, and they ignore the wider health impact for other patients. Considering that the main purpose of health-technology assessments and public reimbursement decisions in many jurisdictions is to maximise population health, the outcome of

assessments may change with an incorrect valuation of opportunity costs of displaced health care resources.

The novel approach proposed in this thesis of the net monetary benefit of the second-best patient forgone aims to quantify those aspects that have not been considered previously for mostly pragmatic reasons. When including these opportunity costs of hospital bed-days into economic evaluations, it is likely that this novel approach will lead to outcomes and incremental cost-effectiveness ratios (ICERs) that favour interventions averting hospitalisations, for as long as the disease is of lesser severity and displaces more severe cases (i.e., the opportunity cost value of the second-best patients is higher). Thus, interventions which otherwise may not have been implemented due to being viewed as too costly may become cost-effective. This is largely due to financial expenditures not approximating to opportunity costs, which is illustrated in Figure 34.

Figure 34. Density per bed-day of the expenditure incurred on norovirus and the net monetary benefit (NMB) of the second-best patients forgone at £20,000/QALY (panel a), and different cost-per-QALY values for the NMB to explore convergence with financial expenditures (panel b).



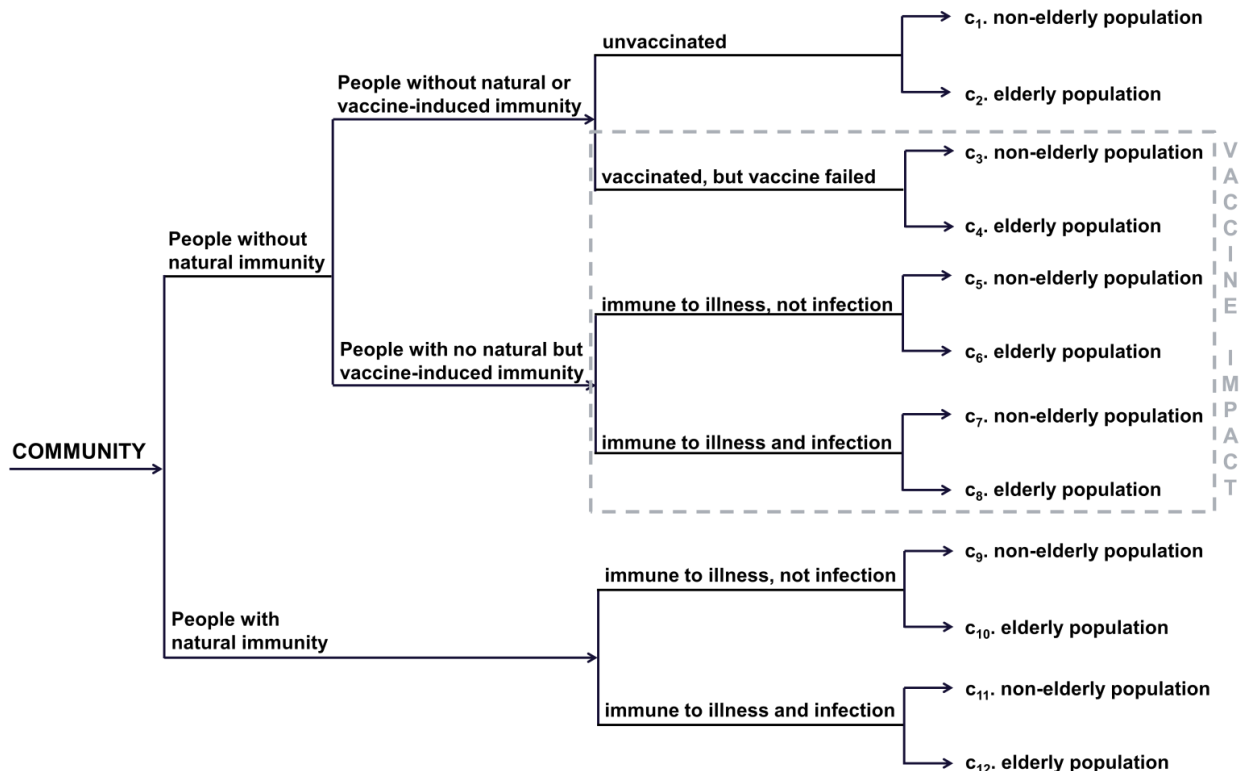
Here, financial expenditures have been estimated to be incurred on norovirus patients per bed-day, resulting from patients, unoccupied bed-days, and staff absences (cf. chapter 4), while the opportunity costs have been estimated as the net monetary benefit of the second-best patients forgone, using the values for the length of stay, QALYs gained and expenditure presented in chapter 4, section 4.10.6, and a monetary value per QALY of £20,000/QALY. In this figure, the financial expenditures incurred would have approximated to opportunity costs at a monetary value per QALY of about £12,978/QALY. However, it is unclear whether the opportunity costs are indeed higher than the expenditure incurred, as suggested here at £20,000/QALY, or whether QALYs are currently being valued too high (as suggested by recent research findings, which suggested that the threshold may indeed be closer to £13,000/QALY).^[150] Given the differences in expenditures by disease area, it is also likely that results will differ for other diseases and in international settings (i.e., the monetary value needs to be lower than £20,000/QALY when financial expenditures are incurred that are lower than the NMB, and higher than £20,000/QALY if the financial expenditures incurred exceed the estimated NMB).

Valuing the opportunity costs adequately is crucial for analyses of the true value of resources to enable sound decision making, as interventions may not get public funding for reimbursement when ignoring these aspects. Future research needs to continue exploring the monetary value assigned to QALYs by different stakeholders and with different techniques. Future studies of economic evaluations and burden of disease estimations should at least make all important assumptions and potential implications of the costing technique used clear and explicit when communicating to decision makers. Researchers need to be aware of the underlying assumptions and resulting biases when applying conventional costing approaches, which frequently are unmentioned and unquestioned or worst: unknown. Moreover, this thesis used rigorous statistical and mathematical modelling techniques for estimating the additional length of hospital stay actually attributable to the infection.^[270-272] However, even if additional length of stay is appropriately estimated any economic evaluation or burden estimation will remain inaccurate (or even misleading) if the value placed on those attributable days is underestimated, or indeed overestimated.^[143]

For norovirus, considering the recurring bed pressures faced by NHS hospitals in England each winter, reducing illness and outbreaks will increase bed capacity that can

be used for otherwise forgone patients. As norovirus has become one of the key enteric pathogens across all ages, particularly in countries that introduced rotavirus vaccination (like the USA,^[164,220] and for the UK see chapter 4), it will become important to evaluate the cost-effectiveness of norovirus vaccination strategies for England in the near future. The potential value of an efficacious norovirus vaccine may be underestimated unless lost bed-days are valued appropriately. The extent of the benefits has been modelled in a recent study of norovirus mass vaccination for the USA,^[308] showing that a total number of 14,100 (95%-CI: 10,100-20,100) hospitalisations may be averted with a pediatric vaccine program, and 4,900 (95%-CI: 3,700-6,000) hospitalisations with routine elderly immunization. The studies presented in this thesis may partly serve as a baseline against which to assess the impact of vaccination for England. Moreover, the model presented in chapter 5 can be extended to explore the impact of vaccine-induced immunity to norovirus infection and/or illness before hospital admission, as shown in Figure 35, which extends the previous Figure 30 with the potential vaccine impact as reflected in the branches labelled with c_3 - c_8 (cf. the grey shaded box in Figure 35).

Figure 35. Classification tree of individuals in the community stratified by age and the natural or vaccine-induced immunity to norovirus infection or illness.

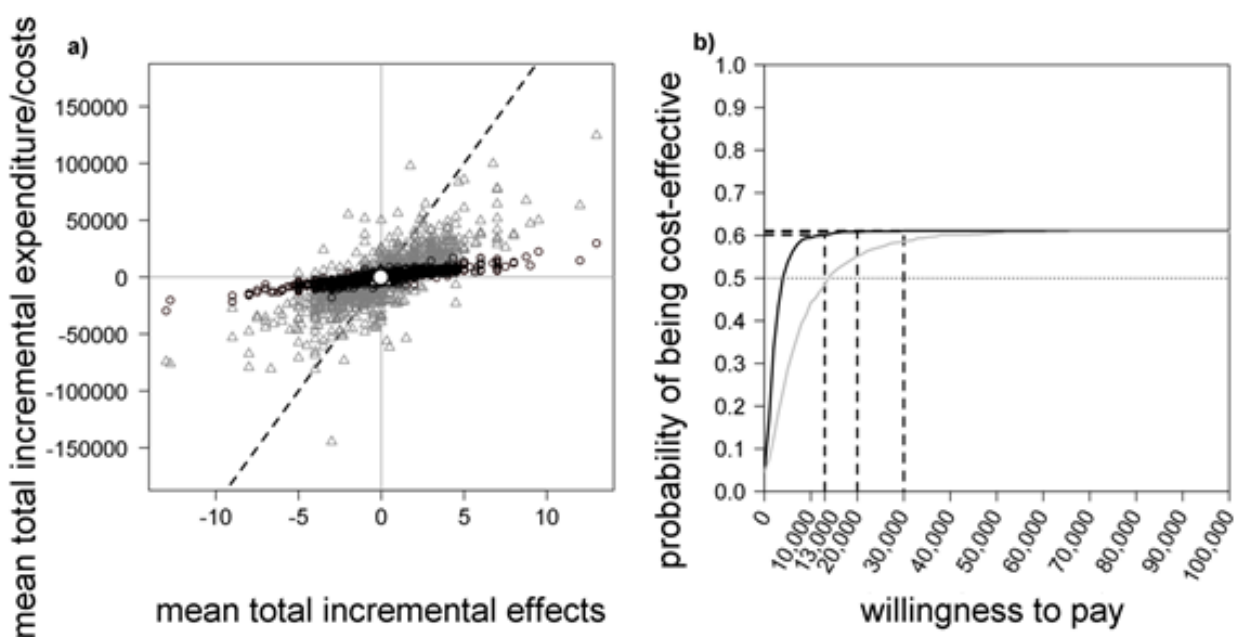


The admission groups for the dynamic model (cf. section 5.4.1.2) could then be extended to:

- i. Admissions unvaccinated and not immune but susceptible to norovirus infection and illness ($c_1 + c_2$);
- ii. Admissions vaccinated but not immune to infection and illness ($c_3 + c_4$);
- iii. Admissions immune (naturally or vaccine-induced) to illness but not norovirus infection ($c_5 + c_6 + c_9 + c_{10}$);
- iv. Admissions immune (naturally or vaccine-induced) to illness and norovirus infection ($c_7 + c_8 + c_{11} + c_{12}$).

These may then feed into a compartmental model (cf. section 5.4.1.3), with separate compartments for the newly inserted admission group ii. of inpatients vaccinated but without immunity, for which all five compartments should be used. The dynamic model could then be combined with the novel approach of valuing bed-days in chapter 2 to estimate the cost-effectiveness of norovirus vaccination (cf. Figure 36), which can be expected to yield diverging results.

Figure 36. Illustrative incremental cost-effectiveness plane (panel a) and cost-effectiveness acceptability curve (panel b) with diverging results when using different cost estimates (shown in grey vs. black).



6.2.1 Comparison of cost estimates for norovirus with other studies

When comparing the estimated results of resources used for norovirus, the study in chapter 4 revealed direct expenditure on norovirus from the healthcare provider

perspective reaching an estimated £107.6 million annually when 1) combining individual-patient data with national hospital statistics and surveillance, 2) accounting for time-dependent biases,^[270-272] 3) looking at all NHS hospitals in England, and 4) accounting for relative changes following the rotavirus vaccination introduction (see sections 4.4.3.1 and 4.5.3.1; note that this estimate did not include the opportunity cost of patients displaced).

The study in chapter 3 also estimated the value of all occupied and unoccupied bed-days lost due to norovirus-like symptoms as £35–£49 million in winter (section 3.6). Assuming that these bed-days represent 52% of all beds lost on norovirus throughout the year (section 4.10.4), scaling these values up to 100% results in £67–£94 million, with the upper bound being £13 million lower than the more accurate estimate of chapter 4. However, the estimate is close to the one calculated based on another study on gastroenteritis outbreaks in hospital in England in 2002/02,^[41] which amounted for norovirus to £96.9 million in 2016 value (cf. section 4.6.2).^[269]

By far the lowest estimates were obtained in a recently published study calculating the societal costs of norovirus for primary care and hospitalisations in England in 2008/2009 using reference costs and income losses of patients.^[275] The total costs for norovirus were £81 million (95%-CI: £63–£106 million), of which 85% were borne by patients and the remaining £11.9–£17.7 million by the healthcare services. The study did not account for time-dependent biases, and it was based on another study attributing about 3,000 hospital admissions annually to norovirus in England.^[273] The study estimated the number of emergency admissions in England due to norovirus in adults with a primary or up to the first 3 secondary diagnoses codes,^[273] while the study in chapter 4 considered patients of all ages with any diagnosis and degree of severity (i.e., not only emergency admissions). Laboratory reports may have also become more reflective of hospital cases in recent years, which may explain why the most parsimonious models resulted in very high adjusted R^2 of 0.98 (cf. section 4.10.2). The previous study reported an adjusted R^2 of 0.89 for patients aged ≥ 65 years, and 0.85 for patients aged between 18–64.^{[273]⁹}

⁹ The authors also investigated including a time variable in their regression to account for any unmeasured effects in improved diagnostics due to the reverse-transcriptase polymerase chain reaction (PCR) replacing the electron microscopy as the main molecular method of detection

Chapter 4 in this thesis is the only study to date that has considered the health opportunity costs of bed-days from patients forgone, with the true costs being equal to up to £297.7 million for the hospitals of the NHS in England. All in all, both the expenditure and costs on norovirus in England are high and above £100 million annually.

6.3 STRENGTHS AND LIMITATIONS

This thesis focussed on the interface between (health) economics and the epidemiology and transmission of infectious diseases. It shed light on an under-researched area in health economics, which may not receive more attention due to lack of awareness among researchers and decision makers about the assumptions of current costing practices. After all, the different existing methodologies of estimating opportunity costs have been shown to have been confusing for professional economists too.¹⁰

Central to this thesis was to scrutinise the current costing conventions applied in economic analyses, which may lead to underestimation of the costs of infectious diseases. This thesis is not the first to point out the shortcomings of the conventional costing approaches,^[4: p.58] but it is first to propose a novel way forward for bed-days and health-maximising decision makers to overcome the issues identified. It also retains a monetary value to allow relative assessments in subsequent economic studies.

For norovirus, an innovative approach was chosen to put different datasources and methods all together to get a comprehensive picture of the hospital burden of norovirus from different angles before contrasting the novel approach to reference costs.

In the following, the strengths and limitations of the novel approach of estimating the opportunity costs of bed-days are discussed before the practical application to norovirus.

between 2001–2006. However, this trend variable did not significantly alter the results; neither did accounting for a time lag or lead of up to 2 weeks for the laboratory data.^[273]

¹⁰ Ferraro and Taylor found that only 21.6% of nearly 200 professional economists and PhD students of economics were able to identify the correct answer on the following question: “You won a free ticket to see an Eric Clapton concert (which has no resale value). Bob Dylan is performing on the same night and is your next-best alternative activity. Tickets to see Dylan cost \$40. On any given day, you would be willing to pay up to \$50 to see Dylan. Assume there are no other costs of seeing either performer. Based on this information, what is the opportunity cost of seeing Eric Clapton? A. \$0 B. \$10 C. \$40 D. \$50”.^[122] The wording and framing of the question have been criticised before.^[123]

6.3.1 Estimating the opportunity costs of bed-days

The novel approach proposed here is in alignment with economic theory by explicitly considering net benefits and effectively re-connecting to the concept of choice (i.e. a “most valuable forgone alternative” exists and needs to be determined, depending on the objective of an decision maker). The approach thereby acknowledges the different resource use by different patients (i.e., the value of a bed-day for one patient is not equal to the value of a bed-day for another patient). Moreover, the approach is broadly applicable across settings and to other diseases.

However, opportunity costs are highly context specific and care needs to be taken with identifying the second-best patient. By considering average data across all national hospitals in England, with different hospital sizes, case mixes and patient characteristics, the strong assumption is made that the average adequately represents the second-best patient forgone. Although this may not be the case, issues of feasibility may justify this assumption (e.g. observing, on a national scale, the actual number of patients displaced). Moreover, one may also argue that average values are reasonable since resource allocation is not perfectly efficient and hospitals do not constantly admit those cases with the highest health need.

6.3.1.1 Delayed versus cancelled admissions

In reality, there may be differences between cases whose admission has been delayed (for a few hours) to those whose admission has been cancelled. Most often, cancelled admission will have an non-urgent/elective component to it.

For determining the value of the second-best patient forgone, this difference may be less pronounced than in clinical practice. It needs to be kept in mind that the second-best patient forgone is used to approximate the alternative value of a bed-day at a particular point in time and place; from an economic perspective, this is the same logic behind the costs encountered in everyday life. Thus, the non-admitted patients do not necessarily need to have been actually delayed or cancelled cases given the interest in only the “value” of the bed-days that could not be used for alternative patients at the time that the opportunity costs arose (at which point the patients were forgone). They may in fact thus be a counterfactual number, which has been hinted to earlier with the wording of alternative admissions as “patient-equivalents” (cf. section 2.5.2).

Hence, cases with the medically least severe/urgent issues do not usually constitute the second-best alternative forgone (but rather the third-, fourth-, ..., last-best treatment alternative, which is seen in practice with the triage system of many hospitals for organising the initial care of unplanned new admissions). Likewise, cases with the medically most severe/urgent issues cannot constitute the second-best alternative (they will likely be the first-best treatment alternative). Therefore, patients with intermediate severity/urgency seem most appropriate to be used as alternative admissions, which have been approximated in this thesis with chronically ill patients as they usually require treatment soon but not at once.

In addition, it needs to be kept in mind that the special situation of infectious epidemic and disease outbreaks were considered in this thesis, which are frequently the cause of seasonal bed pressures. Combined with the presence of waiting lists and high occupancy rates, it seems reasonable to assume that there will be a long list of patients who are actually displaced and could have used the beds instead; at least in acute care hospitals of the NHS in England.

6.3.1.2 Variation in the value of the opportunity costs

Opportunity costs have an inherent link to the concept of choice through the second-best alternative use forgone. For bed-days, this may translate into seasonal and local variation in the value of opportunity costs, and may lead to different estimates depending on the (local) supply and demand for beds. In particular, the value will be higher during times of increased demand, e.g. during winters where the second-best patient is more unhealthy (has greater “need”) than the average patient throughout the year, or during outbreaks where the additional pressure on bed occupancy levels rises. Conversely, the value will be lower during times of decreased demand, e.g. in non-outbreak settings or summers. Likewise, the value can be impacted from the supply side by increasing capacity and thus reducing the actual occupancy rate.

Future research may look more closely at these seasonal and local differences in opportunity costs, if feasible. In addition, tensions may possibly arise when striving for standardised approaches and methods (i.e., it may become more time-consuming to conduct and elaborate on an analysis that differs in its outcome for different settings). Although it seems desirable for the actual costing method to be consistent, the imperfections of the current standards may lead to distorted decisions when the true

impact is greater than currently estimated. Also, shadow prices are already used for non-marketed resources like time and informal care, and price adjustments are generally considered as justified for as long as they follow a clear methodology that is unlikely to introduce substantial bias.^[4: p.58]

Lastly, the thesis focused on demand-side approaches driven by (empirically) revealed data, not on stated-preferences and contingent valuation studies (see e.g. Stewardson 2014 and Page 2017).^[155,309] Other supply-side values for a bed-day may have been obtained by considering the wage rate of over-hours, or e.g. in the UK from the value of £250 per hour plus pension and National Insurance payments of the Waiting List Initiative, which aims at reducing the number of patients on waiting lists by offering additional clinics at weekends and at night.^[193] The reasoning behind these shadow-prices is that the otherwise forgone beds can only be obtained additionally at these marginal costs within the hospital, assuming full capacity. Outside the hospital, further work could also explore interactions between multiple hospitals, e.g. the (transaction) costs of transferrals to a different provider and the value of obtaining a bed in the private healthcare market. However, from most analytical perspectives it is not sufficient to ignore the health impact of the patients forgone who would have otherwise been treated.

6.3.1.3 Monetary value for health gains from hospitalisation

The approach presented in this thesis relies on the existence of a monetary value for health gains. It is acknowledged that this continues to be an active research area, although recent efforts have aimed at estimating such a value for many countries.^[310] Moreover, given the context of reimbursement decision making in England, the main focus rested on QALYs and took the perspective of a decision maker aiming to maximise health with a constrained budget. The monetary value assigned to a QALY (be it the marginal cost of producing a QALY or the consumption value of a QALY) will undeniably drive calculations, and issues of equity have not been explicitly considered here. Although other health outcomes could be used, the same issue applies of finding an appropriate value for the health gains in case it is not seen as sufficient to provide “health outcome”-per-cost metrics.

6.3.1.4 Generalisability

This thesis focused on hospitals and infectious diseases as they provide more complications than non-infectious diseases that make it an interesting example of large and auto-correlated shocks to bed demand. In that regard, non-infectious diseases are less complex and so everything in this thesis still applies to them. Moreover, the proposed ideas are equally applicable for other healthcare facilities or (outpatient/) general practitioner (GP) consultations, and indeed non-healthcare resources. Other facilities with beds for overnight-stays share similar issues as discussed for hospitals in this thesis, while GPs allocate a certain amount of time to their consultation slots and could thus have seen potentially more patients. Non-infectious diseases are also prone to incur opportunity costs, which is most visible for avoidable hospitalisations when patients continue to stay in hospital e.g. for non-medical but social reasons. In terms of non-healthcare resources, one could think of the forgone leisure time and activities for people impacted in the community. There is thus a wealth of potential applications for the ideas presented here.

At present, it is difficult to find studies reporting all of the input data required (as exemplified by the example presented in section 2.9.1). At the very least data are needed on the length of stay, expenditure, and health benefit of treatment for different patients; information that is routinely collected but not fully reported at all times. This may change in the future, not least due to the increasing body of research in the health domain and the economic interest in activities of healthcare systems as well as the increasing number of linkable data sources (which may become important when estimating the second-best patient forgone, particularly in trial-settings with limited scope of alternative patients).

Moreover, it needs to be stressed that in situations where it proves impossible to determine the optimal alternative, or disprove an alternative as non-optimal, it may be preferable to consider only the net monetary benefit of the alternative patients forgone (approach New1; cf. section 2.5.5) and qualitatively acknowledge the distortion in its value from market imperfections.

Lastly, this thesis only looked at one resource within one economic sector. If it was feasible to expand the scope to other resources and across economic sectors, it would technically be possible to pursue allocative efficiency, that is, comparing whether or not it is beneficial to allocate limited resources to interventions across economic sectors.

6.3.2 Application to norovirus

The thesis was also able to demonstrate the economic ideas for estimating the opportunity costs from patients who cannot be admitted due to beds being unavailable by using norovirus-associated gastroenteritis as a case study. It provided updated figures for the hospital burden in England using a range of methods and datasources, which revealed the increased relative impact of norovirus as the second-largest contributor of the gastrointestinal hospital burden in England.

Also, this thesis is first to combine individual-patient data from a norovirus outbreak with national hospital surveillance and routinely collected hospital statistics to apply the novel approach to norovirus. The time-dependent bias was accounted for by considering only the excess length of stays.^[270-272] Thereby, more accurate methods have been used than previously.

Moreover, the datasets used for England captured at least two novel norovirus GII.4 strain emergences, New Orleans-2009 and Sydney-2012,^[58,64] but the burden estimation in chapter 4 focussed on the period after mid-2013 to avoid biased results from the observed heterogeneity introduced by the rotavirus vaccination in July 2013. If a new norovirus strain emerges in future, the burden may likely be higher than the median values of this analysis suggest. Likewise, if an effective vaccine is able to reduce the norovirus burden, the results presented here provide a baseline against which the potential impact of vaccination on hospital bed-days can be evaluated, although the estimations will need to be updated.

This thesis focussed on the economic meaning of costs, not the accounting meaning (i.e., expenditures). As such, expenditures averted on norovirus do not necessarily translate to monetary savings;^[143] it rather means that the resources saved can be redeployed for the benefit of others, e.g. by freeing resources (e.g. beds, personnel time and/or consumables) that become available for alternative uses (e.g. for other patients).

6.3.2.1 Burden of norovirus in hospital versus the community

The main focus of this thesis has been on the opportunity costs of bed-days, which is why the illustration also focussed on the hospital burden of norovirus. However, acute gastroenteritis is a major concern in the community too, not least due to the

interdependencies between community and healthcare facilities (cf. sections 1.3.1 and 1.3.3).

The second Infectious Intestinal Diseases study (IID2) estimated the community burden of norovirus in England with 2.9 million (2.4–3.5 million) cases annually.^[311] A recent study estimated that the number of norovirus infections may reach 3.7 million (3.3–4.1 million) annually,^[274] which is important given the presumed infectiousness of asymptomatic infection owing to the low viral load required for effective transmission (cf. section 1.3.1).

Compared with the estimated 103,000 hospital cases of norovirus in England annually (cf. section 4.5.2.1), the main burden thus clearly appears in the community. However, hospital outbreaks of norovirus are highly disruptive, and they have been estimated to incur significant economic costs internationally.^[41,255-257] With bed pressures being a recurring public health concern, particularly during winters, any analysis considering the impact of diseases like norovirus on hospital systems needs to include the opportunity costs from forgone alternative admissions.

In addition, if outbreaks of norovirus occur in nursing homes or lead to patients visiting their GP, the same methodology can be applied as was done for hospitals here.

6.3.2.2 Generalisability

The statistical and mathematical methods used to quantify the economic burden of norovirus can readily be used for other settings. In fact, regression analyses and multi-state models are widely used, and not just for infectious diseases.

Estimating the opportunity costs of bed-days in terms of the health forgone will require a monetary value per health gain from hospitalisation, specific to the setting. Recent advances have been made to estimate this value for countries globally,^[281] and the concept of the second-best alternative forgone is widely transferable even without a monetary value per QALY.

6.4 CONCLUSIONS

This thesis aimed to explore the true cost of epidemic and outbreak diseases in hospital. The “true” cost of anything is equivalent to the value of the alternative cost, i.e. its opportunity cost, which can be defined as the value of a resource in its highest forgone alternative use. For bed-days, these opportunity costs are fundamental for understanding the value of healthcare systems as they greatly influence burden of disease estimations and economic evaluations involving stays in healthcare facilities.

However, bed-days are an imperfectly-marketed resource, which is why current costing conventions using market prices or average accounting expenditures lead to inadequate shadow prices for the opportunity costs. This holds particularly during epidemics and disease outbreaks when the supply and demand of bed-days are in disequilibrium. Improved capture of relevant opportunity costs seems thus imperative for diseases like norovirus.

Drawing on these findings, a novel approach is presented for estimating the opportunity costs of bed-days in terms of health forgone for the second-best patient, but expressed monetarily. The approach seeks to overcome the issues identified as it consists of the net trade-off cost of the second-best use forgone, and it links explicitly to the economic concepts of scarcity and choice.

For norovirus, the relative burden in hospital has been increasing since rotavirus vaccination introduction in July 2013, with norovirus now being the second-largest contributor of the gastrointestinal hospital burden seen in England. Moreover, the economic impact may have been underestimated by the costing methods that do not capture the opportunity costs adequately. The novel approach estimated two-to-three times higher expected opportunity costs than conventional expenditures. All of this adds to the attractiveness of a norovirus vaccine, although the chosen perspective and costing approach may have a potentially decisive impact for reimbursement decision-making as current costing conventions likely undercost infectious diseases.

Overall, improved capture of relevant opportunity costs seems imperative for diseases like norovirus, and it has been shown to lead to higher estimates in this thesis. Despite this thesis focusing for illustration on hospital-based outbreaks of infectious diseases, the proposed ideas are broadly applicable to other diseases, resources, and settings and likely to increase in future given the increasing number of linkable data sources.

7 APPENDIX

7.1 OPPORTUNITY COSTS AND DIFFERENT SCHOOLS OF THOUGHT IN ECONOMICS

In this thesis I have assumed that it is generally possible for an outside observer to estimate the opportunity costs of resources. This is in line with the neo-classical convention of economics, which accepts that economic behaviours and activities are objectively quantifiable. It has been argued that the subjectivity of demand can still be incorporated in the neoclassical conception of economics: “The dependence of price (value) on marginal utility, subjectively determined, can be fully recognized, while essentially an objective theory of cost is retained. In Jevons' famous statement, marginal utility depends on supply which, in its turn, depends on cost of production. As stated, this theory is wholly objectivist in character, although, of course, the valuation of buyers and sellers is incorporated as a part of the objective data. Costs are objectively determinable, although the theory does not say that costs alone determine value. As contrasted with classical theory, one-way causality is missing, but not the objectivity of the explanation”.^[5: p.11]

However, next to the neo-classical convention exists the so-called “subjectivist” school of thought of economics, which understands economics as an “entirely individualistic and subjectivist concept”^[5]. From this perspective, choices are non-quantifiable for outside observers due to the inherent subjectivity of demand of each individual, and the neo-classical conception of economics is criticised for this lack of choice.^[5] “Cost is measured by the market value of displaced product. Cost is objective in that it can be estimated, at least in *ex post* terms, by external observers, despite the fact that market values are set, generally, by the subjective evaluations by many producers and consumers. Market prices measure collective evaluations at the margins of production, and prices are themselves objective. These statements about cost are widely and uncritically accepted by most modern price theorists, most of whom fail to see that opportunity cost, so defined, has no connection with choice at all.”^[5]

Although the viewpoint of the subjectivist school of economics may have some merit, economics so defined becomes a “purely logical exercise”.^[312: p.7] Unsurprisingly, thus, this school of thought has been widely rejected as impractical by mainstream economists.

It is not favoured in practice, including in this thesis, the main aim of which was to investigate how to estimate the opportunity costs of bed-days adequately (by contrasting the conventional costing practices with a novel proposal), not whether such quantification is even possible (which I believe it is, particularly with revealed preference techniques).

7.2 DISTINGUISHING OPPORTUNITY COSTS, NET BENEFITS (OR ACCOUNTING PROFITS), AND THE ECONOMIC PROFIT

Opportunity costs are equivalent to the net benefit of the second-best alternative forgone (section 2.5.1). They should not be confused with the difference between two net benefits, e.g. of the best and second-best option, as there is a subtle difference in meaning between the two concepts:

The net benefit may also be regarded as the “natural (or accounting) profit” of individual alternatives, and it is calculated as the benefits minus the expenditures. It is also possible to calculate the “economic profit”, which is the difference of the highest accounting profit of the optimal alternative and the second-highest accounting profit of the second-best alternative. Opportunity costs are equal only to the second-highest accounting profit.

To illustrate, O’Donnell (2010)^[34] gives the example of four different occupations (p. 5):

- independent entrepreneur (with annual revenues: AU\$240,000, expenditures: AU\$170,000, and thus an accounting profit of AU\$70,000),
- manager (wage: AU\$50,000, expenditures: AU\$0),
- programmer (wage: AU\$60,000, expenditures: AU\$0),
- teacher (wage: AU\$40,000, expenditures: AU\$0).

Faced with these four alternatives, the best decision is being an independent entrepreneur with a net benefit of AU\$70,000 (the highest valued occupation), with opportunity costs of AU\$60,000 (the highest valued alternative forgone) and an economic profit of AU\$10,000 (the accounting profit of highest valued occupation *minus* the second-best alternative forgone).

Translating this to bed-days, the difference between different net benefits may indicate the potential economic loss associated with not taking the optimal course of action (and thus e.g. indicate the health outcome lost when giving up a bed-day during an outbreak).

Looking specifically for norovirus the alternatives investigated were (section 4.10.8):

- Norovirus cases (with annual [gross monetary] benefit: £150.2 million, expenditures: £107.6 million, and thus an accounting profit of £42.6 million),
- Non-gastroenteritis patients (with annual [gross monetary] benefit: £276.2 million, expenditures: £86.1 million, and thus an accounting profit of £190.1 million).

If one was to assume for a moment that these two patient groups are each other's next-best alternative (which is unlikely to be true for the norovirus patients, who will not be the next-best alternative of the non-gastroenteritis patients), then the optimal treatment choice would be the non-gastroenteritis patients at a net benefit of £190.1 million, with opportunity costs from the norovirus cases of £42.6 million and an economic profit of £147.5 million (the estimated net benefit achievable of £190.1 million *minus* the expected opportunity costs of £42.6 million).

However, given that the non-optimal alternative of norovirus cases were treated in reality at an estimated net benefit of £42.6 million, the opportunity costs rise to 297.7 million (£107.6 million *plus* £190.1 million) when accounting for the optimal net benefit forgone from the non-gastroenteritis patients, and the economic profit turns into an economic loss of -£255.1 million (the estimated net benefit achievable of £42.6 million *minus* the expected opportunity costs of £297.7 million).

Moreover, opportunity costs are not equivalent to any trade-off costs. The net benefit forgone from the norovirus cases of £42.6 million represents the “trade-off costs” of these two options rather than the opportunity costs. In practice, many comparisons may identify “trade-off costs” of two different interventions or actions as the opportunity costs.^[34] Implicitly or explicitly, the assumption is being made that the chosen comparator(s) involve the available alternatives and the opportunity costs will be determined from the other alternative. Based on this assumption, the true opportunity costs will not just be the value of any different resource use: Only the alternative with the second-highest value among a range of alternatives qualifies for being the second-best alternative (hence the qualification in Adam Smith's example to consider a nation of hunters and two animals; no other occupation nor animals exist that may provide a higher value).^[5]

In such circumstances, the term “opportunity costs” should be used with caution given its inherent link to a valuation ranking of multiple alternatives.^[34] O'Donnell (2012) advised referring to “trade-off costs” instead as the true opportunity cost is always a trade-off cost, but not all trade-off costs will be opportunity costs.^[34]

7.3 DECISION-ANALYTICAL MATHEMATICAL MODELS

Decision-analytical models aim to explore a decision problem under uncertainty.^[124] Although the gold standard in healthcare is to base decisions on randomised controlled trials (RCTs), such studies may not always be available and compare all relevant alternatives over a sufficiently long time horizon for a representative population.^[124,313] Decision-models can help overcome these issues, and also bridge the gap from individuals to populations.^[313] Generally, the most frequently used modelling techniques can be summarised as follows (of which this thesis used a multi-state model as part of chapter 4, and a compartmental model in chapter 5):

1. The “decision tree” model follows a flowchart-like structure of different options with probabilities for their associated outcomes and expenditures.^[314] It is most suitable for non-recurring events in patient (sub-)populations and short time frames.^[124]
2. The “multi-state model” represents different options with the associated (health) states that can be occupied recurrently by individual (sub-)populations over time. In case future states only depend on the current state and not previous ones, this is called the “memoryless” Markovian property and the multi-state model often referred to as a “Markov-model”. This property may be avoided with a sufficiently large number of states though to the disadvantage of computational performance.^[124]
3. The “individual agent-based model” tracks each individual person in the model separately. This micro-simulation approach allows each agent (e.g. patient) to occupy and change states separately according to different probabilities,^[124] which enables specifying in greater detail e.g. disease histories.^[315] However, this approach is computationally demanding and rises the question of whether the patient heterogeneity cannot be captured by other modelling techniques that aggregate individuals with similar characteristics into sub-groups.^[124]
4. The “discrete event model” is a form of micro-simulation that is not continuously progressing but only discretely when an event occurs. The state of the model thus does not change in between events. The model allows for tracking individuals, which increases the computational burden.^[124,314]
5. The “compartmental model”, or “system dynamic model”,^[314] tracks aggregated sub-groups of individuals in different compartments representing health states. The rate of change between compartments is described by a set of ordinary differential equations, ODEs.^[316] The application of compartmental models to infectious diseases originates from a paper of Kermack and McKendrick,^[294] who described the three health states of susceptible, infected, and recovered/removed by death (SIR-model) to explore the plague mortality on an island in India in 1905/1906. These types of models are indeed also most widely used for modelling infectious disease dynamics.

Note that these modelling techniques may also be combined; e.g. a Markov model with subsequent decision trees.^[124]

Each of these models may follow a deterministic or stochastic structure. Deterministic models will always result in the same values due to fixing parameters and disregarding any chance variation, while stochastic models take random chance into account and may thus reflect natural processes more accurately,^[316] particularly when looking at small numbers or short time frames.^[315]

Models differ for infectious and non-infectious diseases due to the non-self-limiting nature of contagious diseases arising from possible transmission of pathogens¹¹ but also the indirect protection through “herd immunity”.^[37,316] Models that include these indirect effects of vaccination are usually called “dynamic” or “transmission-dynamic” as they account for a reduced number of infectious individuals in a population over time given that the risk of transmission is dependent on the number of infected people (i.e., the force/rate of infection).^[313] Otherwise if the force of infection is treated as an exogenously-set fixed parameter, the model is said to be “static”.^[316]

Different algorithms exist for helping analysts choose the appropriate modelling technique,^[124,314,316] although the most adequate model will be the most parsimonious one.^[314] Moreover, all models – regardless of animal, healthy volunteers or mathematical – are a simplification of the complex reality. Thus, as famously stated by George Box repeatedly: “Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful.”^[318]

¹¹ An important metric for infectious diseases is the “basic reproduction ratio”, abbreviated with R_0 : It represents the average number of secondary cases infected by a typical case during the period of infectiousness in a completely susceptible population.^[317] If transmission generates less than one new case, i.e. $R_0 < 1$, the infection will not be able to establish itself and die out, while otherwise when generating more than one new case, i.e. $R_0 > 1$, the infection sustains in a population and may result in outbreaks and epidemics (unless considering stochastic extinction).^[317] Typical estimates of the basic reproduction ratio for different infectious diseases are $R_0 = 2-4$ for influenza, $R_0 = 12-18$ for measles, and $R_0 = 5-100$ for malaria.^[293]

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