Variation of stroke-associated pneumonia across the United Kingdom and its impact on clinical outcomes

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

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List of abbreviations

ACEI – Angiotensin Converting Enzyme Inhibitors

AHA – American Heart Association

AIS – Acute Ischaemic Stroke

ATSIDS – American Thoracic Society and Infectious Disease Society

CAP – Community acquired pneumonia

CDC – Centers for Disease Control and Prevention

CHF – Congestive Heart Failure

CI – Confidence Interval

CNSR – Chinese National Stroke Registry

COPD – Chronic Obstructive Pulmonary Disease

DARF – Data Access Request Form

DARG – Data Access Request Group

DSPT – Data security and Protection toolkit

HAP – Hospital acquired pneumonia

HES – Hospital Episode Statistics

HQIP – Healthcare Quality Improvement Partnership

HR – Hazard ratio

H2A – H2 antagonists

ICC – Intraclass correlation

ICD – International Statistical Classification of Diseases and Related Health Problems

ICH – Intracerebral haemorrhage

ICSWP – Intercollegiate Stroke Working Party

IRR – Incidence rate ratio

IV - Intravenous

LACI – Lacunar infarction

LOC – Level of consciousness

MCA – Middle cerebral artery

mRs – Modified Rankin Scale

NCAPOP – National Clinical Audit Programme

NG – Nasogastric

NICE – National Institute of Health and Care Excellence

NICU – Neurological Intensive Care Unit

NIHSS – National Institute of Health Stroke Scale score

OCSP – Oxfordshire Community Stroke Project

OR – Odds ratio

ONS – Office of National Statistics

PACI – Partial anterior circulation infarction

PEDW – Patient Episode Database for Wales

PISCES – Pneumonia in stroke consensus group

POCI – Posterior circulation infarction

PPI – Proton Pump Inhibitors

RCT – Randomised controlled trial

RR – relative risk

Rr – Respiratory rate

RWD – Real World Data

SAP – Stroke associated pneumonia

SLT – Speech and Language Therapist

SIGN – Scottish Intercollegiate Guideline Network

SSNAP – Sentinel Stroke National Audit Programme

TACI – Total Anterior Circulation Infarction

TIA – Transient Ischaemic Attack

TOAST – Treatment of ORG 10172 in Acute Stroke Treatment

WHO – World Health Organization

VAP – Ventilator Associated pneumonia

Abstract

Stroke associated pneumonia (SAP) occurs in 8%-14% of people admitted with a stroke. Prevalence of SAP varies considerably across the world, with various frequencies reported among registries and observational studies; however, there is no evidence explaining how SAP varies across stroke units nor what the potential reasons for this variation are. There is also no evidence suggesting how SAP variation affects clinical outcomes. This thesis aims to fill these gaps in knowledge by focusing on 4 different aspects:

- to describe the variation of SAP across England and Wales and determine how much of the variation can be accounted by clinical characteristics;
- to describe the relationship between SAP and specific stroke care processes in the pre-hospital, hyperacute and acute phases;
- to explore the different characteristics used by clinicians to initiate antibiotics in SAP;
- to explore the relationship between SAP and clinical outcomes.

The first study of this thesis was a registry based cohort study that analysed SAP variation across stroke units in England and Wales, using individual patient level registry data. Median SAP prevalence was 8.5% (IQR 6.1 – 11.5%). SAP probability was calculated for each stroke unit, as well as variance. The mean and variance of predicted SAP probability decreased from 0.08 (0.68) to 0.05 (0.63). This suggests that patient characteristics account for 5% of the observed variation of SAP across stroke units in England and Wales.

The second study of the thesis was also a registry based cohort study that analysed the relationship between timings of certain stroke care processes and the development of SAP across stroke units in England and Wales. Increased times to arrival at a stroke unit, increased time to assessment by a specialist doctor and increased time to assessment by a physiotherapist were associated with increased odds of SAP. Shorter times to thrombolysis were associated with lower odds of SAP.

The third study of the thesis was a cross –sectional survey of UK stroke clinicians exploring the different characteristics and thresholds clinicians use to diagnose and initiate antibiotics for suspected SAP. It was an online survey conducted from December 2019 to February 2020. I found that clinicians use known factors such as inflammatory criteria for diagnosis and antibiotic initiation. I also found that the thresholds for each of these factors varied between clinicians, suggesting a lack of standardisation of SAP diagnosis and antibiotic initiation.

The final study of the thesis was a registry based cohort study analysing the relationship between SAP and clinical outcomes. I focused on patients whose length of stay in hospital was > 7 days. By focusing on this specific population, potential confounding due to stroke severity on clinical outcomes was mitigated. SAP was consistently associated with increased risk of longer length of stay in hospital with an incidence rate ratio of 1.27 (95% CI 1.25 to 1.30), worse functional outcome at discharge with an odds ratio of 2.9 (2.9 to 3.0) and increased risk of in-hospital mortality with a hazard ratio of 1.78 (1.74 to 1.82).

The work presented in this thesis has demonstrated how SAP has important variation across stroke units in England and Wales, and that there are modifiable factors that could be contributing to this observed variation. It has also confirmed the adverse association between SAP and clinical outcomes in real-world stroke unit care. This thesis is the platform for future work to develop a new intervention or tool to reduce the burden of SAP in the UK.

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Declaration

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No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

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I would like to first thank my family for their continued support from the other side of the world. Without their encouragement and positive words, I would've struggled a lot more. I would also like to thank my fiancé Adriana for her constant love, understanding and bearing with me for these three long years apart.

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Statement of contribution

Professor Smith, Professor Vail and Dr Benjamin Bray were involved in the initial concept of the PhD project. I was involved in the design, analysis, interpretation and writing up of initial drafts of all chapters of this thesis. I was also in charge of requesting and transferring the data from SSNAP, as well as any governance surrounding HQIP and SSNAP. I was in charge of all data analytics, coding and STATA programming used to analyse the data of this project. I was in charged in the design, initial draft and concept of the survey used in chapter 5. Professor Smith, Professor Vail, Dr Bray and Dr Gittins aided in the editing of each chapter. Dr Gittins helped in the data analytics, corrections in coding and data interpretation.

List of published works from this thesis

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List of abstracts presented from this thesis

Variation of stroke-associated pneumonia in stroke units across England and Wales – ESOC 2020

Variation of stroke-associated pneumonia in stroke units across England and Wales – UKSF 2020

Exploring markers of stroke care and stroke associated pneumonia in stroke units across England and Wales – ESOC 2021

Investigating stroke care processes and their association with stroke associated pneumonia – UKSF 2021

How do clinicians approach diagnosis and antibiotic initiation in stroke associated pneumonia? A UK cross-sectional study – UKSF 2021

Chapter 1 – Introduction

1.1. Stroke

Stroke is historically defined as: "a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 2 hours or leading to death." (1) (2, 3). This definition is used by the World Health Organization (WHO), the National Institute of Health and Care Excellence (NICE) and the Scottish Intercollegiate Guideline Network (SIGN) (4). The American Heart Association (AHA), in 2013, published an expanded definition to include different types of cerebrovascular disease (5). Among these include the categories of cerebral infarction, subarachnoid haemorrhage, ischaemic stroke, intracerebral haemorrhage, stroke caused by cerebral vein thrombosis and definition of stroke not otherwise specified.

Pathophysiologically stroke is divided into 2 different categories: ischaemic or haemorrhagic. The aetiology, causation and mechanisms of injury for both are different, and as such, the treatment and management approach to each in the early stages of stroke are fundamentally different, but with some overlap (6). An ischaemic stroke occurs when the blood flow to the brain tissue is interrupted by a thrombus, usually thrombo-embolic, associated with artery to artery embolism or cardioembolism (7), or by a critical reduction in cerebral flow. A haemorrhagic stroke occurs when there is a rupture of a blood vessel or vascular abnormality, or due to haemorrhagic transformation of an ischaemic stroke (8). Ischaemic strokes can be subdivided using the 2017 TOAST (Treatment of Org 10172 in Acute Stroke Treatment) classification as follows: 1) large artery atherosclerosis, 2) cardioembolism, 3) small vessel occlusion, 4) stroke of other determined aetiology, 5) stroke of undetermined aetiology (9). Ischaemic stroke is far more common than haemorrhagic stroke, generally accounting for around 80-85% of all strokes, while haemorrhagic subtypes account for 15-20% of all strokes (10). However, patients with haemorrhagic stroke, specifically intracerebral haemorrhage (ICH), have worse outcomes; such as a higher mortality, worse sequelae such as lower recovery rates, lower mobility, increased risk for aphasia and longer recovery time, compared to patients with ischaemic stroke (8)

Stroke type	Ischaemic	Intracerebral Haemorrhage
Mechanisms	Cardioembolism Artery-artery embolism In-situ thrombosis Haemodynamic	Rupture of abnormal artery Rupture of vascular abnormality Bleeding diatheses
Examples of **underlying causes**	Atrial fibrillation Atherosclerotic plaque rupture Arterial dissection Pro-coagulant states Cerebral small-vessel disease	Microvascular angiopathy (eg, amyloid angiopathy Aneurysm Arterial-venous malformation Treatment with anticoagulants
Prevalence	80-85%	15-20%
Mortality	10-15% (3 month follow-up)	55-59% (3 month follow-up)

Table 1.1.1 Comparison between Ischaemic and Haemorrhagic stroke, with mechanisms and precipitating factors, prevalence and mortality rates (11)

1.1.1. Presentation of Stroke

Stroke is heterogeneous in its presentation, as it depends mainly on which vascular territory and cerebral regions are involved, as well as the extent and duration of cerebral ischaemia. Facial droop, arm weakness and abnormal speech are the most common clinical manifestations of stroke. These characteristics are part of the FAST assessment developed by the AHA, which state that if one of these symptoms is positive, the probability of the patient having a stroke is 72% (12). Other manifestations of stroke include visual field defects (monocular or homonymous), problems with articulation and language, dysphagia (swallowing issues), sudden loss of balance, and sensory problems, among others (13).

The patient's clinical presentation can suggest which region of the brain and vascular territory is affected, which influences the clinical outcome of the patient. The Oxfordshire Community Stroke

Project (OCSP) was developed to aid in classifying the different stroke syndromes based on clinical and neuroanatomical aspects. These 4 subtypes are Total Anterior Circulation Infarcts (TACI), Partial anterior circulation infarcts (PACI), Posterior circulation infarcts (POCI) and Lacunar infarcts (LACI). TACI typically includes ischaemia in both the deep and superficial territories of the middle cerebral artery, PACI consists of the more restricted cortical or subcortical infarcts in the MCA or anterior cerebral artery (ACA), and POCI is associated with infarction in the vertebro-basilar territory involving the brainstem, thalami, cerebellum or occipital lobes (13). LACI are distinct entities caused when there is ischaemia in the territory of a single perforating artery (14). TACI are generally severe stroke as they involve the full middle cerebral artery (MCA) territory, whereas PACI tend to be less severe (7). LACI and POCI patients generally have the most variable outcomes compared to patients who fall under other syndromes, which range from minor to severe (14).
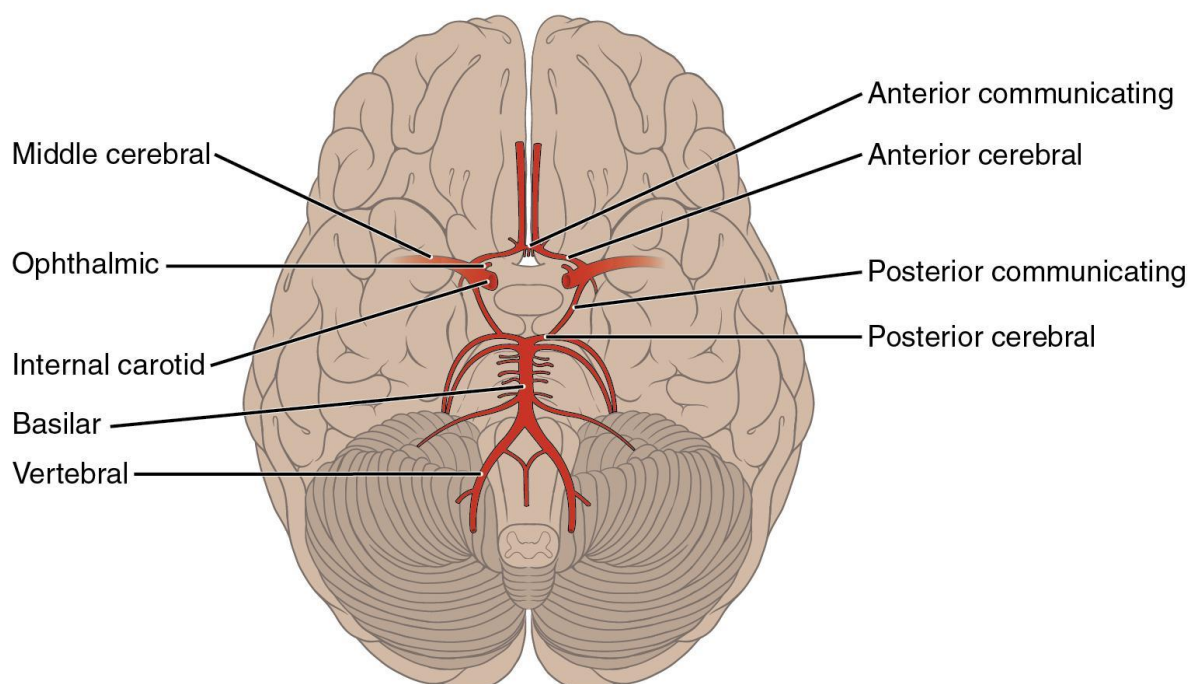
Figure 1.1.1 Brain vasculature [taken from Emedicine.medscape.com. (2019). *Circle of Willis Anatomy: Overview, Gross Anatomy, Natural Variants*. [online]

1.1.2. Stroke risk factors

The Framingham study, an observational study that started in the 1970s and continues to this day, has helped to shed light on the main (conventional) vascular risk factors for stroke. These are systolic blood pressure, presence of cardiovascular disease, presence of left ventricular hypertrophy, current smoking status, current or previous atrial fibrillation and diabetes mellitus (15). These can be divided into 2 different categories, modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, current or previous atrial fibrillation and presence of untreated left ventricular hypertrophy. Among the modifiable risk factors are current smoking status, systolic blood pressure and diabetes mellitus (10).

1.1.3. Epidemiology of Stroke

Stroke is among the most common causes of cardiovascular death worldwide; for example, strokes have a prevalence of 2.6% in the US (16), and in the UK, there are over 100,000 new strokes diagnosed per year (17). According to the WHO, in 2012, there were an estimated 6.7 million deaths worldwide due to stroke (18). Although the incidence of stroke in developed nations is still among the highest in the world, incidence rates over the past years have reduced. However, occurrences in the developing world, such as India, Russia, Ukraine, Brazil or Georgia, have increased, with mortality in the developed world decreasing (19). Whilst there is a statement to be made that incidence rates will decrease with improved healthcare, projections are that overall incidence rates will increase with the continued ageing of the population (20, 21). Even though case fatality of incidence mortality in stroke is still high, there are now more survivors worldwide, meaning that patients with sequelae are more frequently surviving, thus increasing the burden on the healthcare and social systems of each country. For example, the prevalence of stroke survivors in England was 1.80%, with 1,086,155 patients living with stroke as of 2019 (22). As such, stroke remains one of the most important non-communicable diseases worldwide (16). The high prevalence of this disease has its impact on healthcare systems worldwide, with important economic ramifications. A study by Xu et al used data from the Sentinel Stroke National Audit Programme (SSNAP) in a predictive model to

calculate and predict the cost of stroke in the UK, excluding Scotland. They found that one stroke patient costs the NHS £46,039 in 5 years. With this model and prediction, they calculated the cost in total for all stroke patients was £1.74 billion per year, and a total of £3.60 billion in 5 years(23). The huge economic cost that stroke presents to the world is just one of the consequences demonstrating the impact of this condition.

1.1.4. Management of stroke

Management of stroke can be considered as that occurring in the first hours (hyperacute), the first days (acute) and longer term (weeks to years). The hyperacute and acute management of stroke has been summarized by various guidelines using existing evidence, opinion and consensus. In England, Wales and Northern Ireland, the NICE guidelines are the national standard for treating patients with stroke (6). The management of stroke can be broadly divided into 2 different stages: hyperacute/acute care and rehabilitation. Hyperacute/acute care comprises rapid assessment, diagnosis and urgent medical or surgical treatment, while rehabilitation includes in-hospital and community multidisciplinary care (24, 25). A central component of hyperacute care is that the patient with a suspected stroke is rapid assessment and triage at scene and rapid transfer to an appropriate environment with relevant facilities (e.g. hyperacute stroke unit or HASU) for assessment and management by expert healthcare professionals.

1.1.4.1. Hyperacute and acute management of stroke

Once in the emergency department or HASU, there are several processes that take place in order to confirm diagnosis of a stroke and initiate timely treatment. Time is of the essence in hyperacute management of stroke; patients with a suspected acute stroke should receive brain imaging urgently, at most within 1 hour of arrival at hospital. Rapid deployment and interpretation of acute stroke imaging is used to triage urgent intervention or direct appropriate management of stroke mimics (e.g brain tumour or subdural haematoma). Selected patients with non-haemorrhagic stroke are considered for thrombolysis, and those with large-vessel occlusion (e.g. on CT angiography)

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should be considered for mechanical thrombectomy, but this should not delay the administration of thrombolysis (6). Patients who arrive within 4.5 hours from symptom onset to hospital are eligible to receive thrombolysis. The key message is that speed is essential for better outcomes for stroke patients.

With regards to haemorrhagic stroke, the acute management of intracerebral haemorrhage include anticoagulant reversal, if applicable, lowering of blood pressure, level of consciousness monitoring, and neurosurgical intervention if indicated (26).

Hyperacute and acute care also comprise other important measures to optimise physiological variables and reduce complications. Clinical monitoring, particularly level of consciousness, blood glucose, blood pressure, O_2 saturation, hydration and nutrition, temperature and cardiac rhythm and rate are important components (6). Other important measures include a swallow test to screen for dysphagia, which in the UK generally takes place in 2 phases. The first is a bedside swallow screening within four hours of admission into the stroke unit, by an appropriately trained individual (usually a stroke nurse) using a standardised assessment, followed by a more comprehensive assessment by a speech and language therapist (SLT) within 72 hours of admission if required. After dysphagia is established, the most important measure is to avoid or restrict oral fluid and food intake and to evaluate this further and establish alternative means to receive nutrition, medication and hydration, with intravenous (IV) fluids and nasogastric (NG) tube as options (6). Finally, should treatment fail, palliative care measures should be adopted by the stroke care team.

1.1.4.2. Rehabilitation management of stroke

Rehabilitation is one of the most important steps in improving patient outcomes, and involves a multidisciplinary team of healthcare professionals including physicians, physiotherapists, occupational therapists, SLTs, rehabilitation nurses, social workers and psychologists, among others (25). The rehabilitation measures that stroke units adopt are utilised to tackle the different possible sequelae, with special measures being to address arm function, cognition, communication,

continence, fatigue, hydration and nutrition, mental capacity, mobility, mood and well-being, mouth care, pain, sensation, sex, spasticity and contractures, swallowing and vision (6). Potential long-term complications are addressed in the measures mentioned in the NICE guidelines, but the most important thing to note is that all are initiated within a stroke unit by a dedicated, trained stroke team. This process also continues after discharge, with community neurorehabilitation services and early supported discharge.

While all stroke units have different staffing and approaches, it has been shown that admission to a stroke unit improves outcomes in patients. A systematic review published by The Stroke Unit Trialists Collaboration in 2013 found that patients who received inpatient care in a stroke unit had lower mortality, more independence and a higher chance of being discharged one year after stroke compared to patients who did not receive this attention (25, 27). Possible explanations for the better outcomes associated with stroke unit care could include the extra training and dedication the staff who mans these units, as well as the adoption of specific care protocols dedicated to stroke patients compared to general medicine or NICU units.

1.2. Stroke Associated Pneumonia

1.2.1. Pneumonia definition

According to NICE guidelines, pneumonia is defined as an infection of the lung parenchyma, usually caused by microorganisms such as viruses and bacteria, with bacterial pneumonia being much more frequent in adults than viral pneumonia (28). It is usually diagnosed using several criteria, including clinical, laboratory and imaging features, such as fever, tachypnoea, chest x-rays, biomarkers such as procalcitonin or c-reactive protein and blood and sputum cultures (29).

Pneumonia is classified depending on the clinical setting or environment in which it occurs, which is related to likely micro-organism exposure. The Centre for Disease Control and Prevention (CDC) in the USA uses the following classification: Clinically defined pneumonia, pneumonia with specific laboratory findings and pneumonia in immunocompromised patients (29). This classification is

different than that used in England, Wales and Northern Ireland, where NICE guidelines are advocated. NICE guidelines classify said infection into different categories: community acquired pneumonia (CAP), hospital acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (30). CAP is defined as all lower respiratory tract infections that occur outside a hospital setting, up to the first 48 hours of admission to hospital from the community (31). Hospital acquired pneumonia is defined as any lower respiratory tract infection 48 hours after admission (32). Ventilator-associated pneumonia is defined as a lower respiratory infection that occurs in patients in the ICU who have been mechanically ventilated in the past 48 hours (32).

Pneumonia and lower respiratory tract infections have long been recognized as important complications of stroke (33, 34). However, the terminology and definitions used (eg. chest infection, post-stroke pneumonia, aspiration pneumonia) have been variable between different studies (35, 36). The Pneumonia in Stroke Consensus (PISCES) group in 2015 proposed consensus operationalised recommendations for the terminology and classification of pneumonia and respiratory tract infections complicating stroke. Stroke-associated pneumonia (SAP) was defined as follows: "SAP is the recommended terminology for the spectrum of pneumonia complicating the first 7 days after stroke onset in non-ventilated patients" (37). This definition covers a broad spectrum of pneumonia; however, past definitions of SAP include that from 2003, in which SAP was defined as the CDC criteria of lower respiratory infection within 72 hours of admission into the Neurological Intensive Care Unit (NICU) (29). Comparing the two, the PISCES group definition extends the time scale of the diagnosis of SAP to one week compared to the first 72 hours. This extension was probably due to the variation discovered in a systematic review performed by Kishore et al. in 2015 (35), which found that the terminology being used was inconsistent. It is important to note that the definition of SAP by the PISCES group uses the CDC criteria for the diagnosis of pneumonia, which links to the existing definitions of pneumonia previously used in HAP, CAP and VAP. With the current overlap between CAP, HAP and SAP, it is very important to highlight the differences between them. SAP needs to be considered as a separate entity to CAP and HAP due to several important differences. Firstly CAP

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commonly precedes stroke and HAP commonly complicates stroke. SAP occurs most commonly within the first 72 hours after stroke, and its development is aided due to the frequent dysphagia present in stroke patients and transient immunosuppression by the stroke itself. Another important difference to highlight is that the microbiological entities found in SAP are likely polymicrobial because pneumonia within the first days of a stroke would involve microorganisms commonly found in HAP and CAP, which leads to the development of new terminology. The pathophysiology of SAP is discussed further along in chapter 1.2.4.

-2	-1	0	1	2	3	4	5	6	7

Community Acquired Pneumonia

Stroke Associated Pneumonia

Hospital Acquired Pneumonia

Stroke/admission
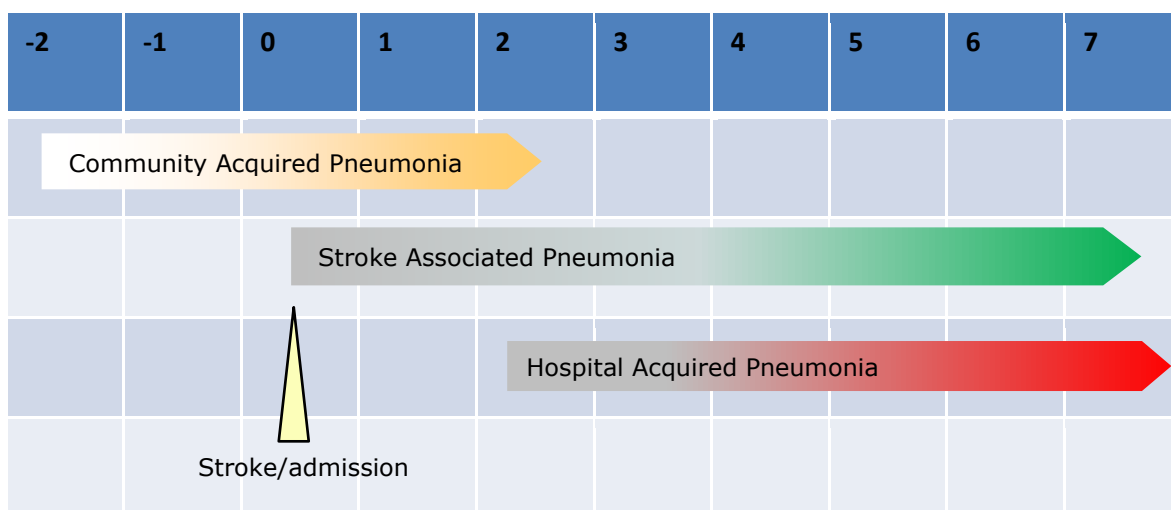
Figure 1.2.1. Figure showing the overlap of the definitions of pneumonia with stroke associated pneumonia. Each cell is equal to 24 hours

1.2.2. Epidemiology of SAP

SAP has been studied worldwide, including South East Asia (38-40), Europe (41-44) and the United States (34). However, the frequency of SAP in each study differs. Pneumonia complicating stroke most commonly occurs within 72 hours after stroke, which could be one of the factors contributing to the variation of frequency between different studies and registries. For example, a systematic review by Kishore et al showed frequencies of SAP between 6.7% and 50.5% (36). A systematic review done by Westendorp et al in 2011 reported that the frequency of pneumonia after stroke

was 10%, however this increased in ICU up to 46% (45). A more recent systematic review (46),

reported an overall frequency of pneumonia at 14.3%, while the most recent available Sentinel

Stroke National Audit Programme (SSNAP) audit registry data places frequency at 8.1% (47). Another

explanation for the observed variation could be the characteristics of the studied population. The

characteristics of each population studied have the potential to be different from one another and

this could be reflected in different frequencies. For example, the prevalence of the different risk

factors associated with pneumonia could be very frequent in a certain population, for example,

populations that are associated with increased smoking habits could have a higher prevalence of

pneumonia compared to populations where smoking in public places is banned (48, 49). Another

important aspect would be seasonal changes, which could affect the frequency of pneumonia (50,

51). One example can be seen in the SSNAP reports of different seasons, where the frequency of

pneumonia is 8.1% in the months of April-June and July-September, but when looking at the reports

of December 2017-March 2018, the frequency increases to 9.3% (47). It is important to note that

there are differences when analysing data from existing registries or cohorts and bespoke research

studies. The latter usually focus on a specific selected population, for example acutely dysphagic

patients with ischaemic stroke in a 2-year period meeting particular eligibility criteria, while

registries generally have no selection bias, as all patients are intended to be included in the dataset.

Another factor which can explain the differences between SAP frequency can be priorities of the

registries themselves. Registries record information based on the priorities and consensus of the

governing health bodies, for example the Chinese National Stroke Registry (CNSR) records

information based on what the Ministry of Health of China determines (52), while SSNAP records

what the Intercollegiate Stroke Working Party (ICSWP) defines (53). The priorities of governing

health bodies could vary, and lead to a variation of frequency of SAP across different registries due

to differences in design of registries and therefore data collection. Another factor that should be

taken into account is how physicians are diagnosing SAP. This includes the definition that physicians

are using to describe SAP, the methodology used to diagnose SAP (such as clinical criteria or an

algorithm used) and if measures are in place to prevent SAP or not. Medical practices regarding SAP are not standardized, which can lead to a high variation in the diagnosis and recorded prevalence of SAP (35). This was shown in the systematic review and meta-analysis done by Kishore et al, which found that clinicians used three main criteria to diagnose pneumonia: the Centre for Disease Control criteria, the Mann criteria and the American Thoracic Society and Infectious Diseases Society (ATSIDS) (35). However, they also showed that many studies did not use any defined criteria or used ad hoc criteria which had not been previously published. This variation in criteria can lead to a disparity of the prevalence of SAP, which can result in a misuse of antibiotics in an era where antibiotic resistance is an ever-increasing threat to healthcare systems across the globe (54).

1.2.3. Risk Factors and predictors of SAP

A number of risk factors have been reported for SAP. Risk factors are, according to the WHO: "… any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury." (55). Pneumonia risk factors between populations have several important differences that are important to highlight. Risk factors for CAP have been reviewed in many studies. Almirall et al, in his 2017 systematic review showed evidence that age, smoking habit, environmental exposure, poor nutritional status, functional impairment, chronic bronchitis/COPD, asthma, previous CAP, poor oral health, immunosuppressive therapy, oral steroids and treatment with proton pump inhibitors or H2 antagonists are risk factors for CAP in adults (56).

In HAP, the risk factors vary depending on the patient's physical environment. Among the risk factors that have been reported are duration of hospital stay and severity of underlying illness, as described by Lynch in 2001 (57), however, a more complete review of HAP done by Leroy et al provided a more descriptive break-down of different factors into three different categories: patient-related, technique-related and pharmacologic-related risk factors (58). Among the patient-related factors are immunosuppression, aspiration, chronic respiratory insufficiency and chronic neurologic diseases.

SAP risk factors, taking into account the definition proposed by the PISCES group, might overlap with both CAP and HAP, however, there are distinct differences when comparing the three types of pneumonia. The similarity with HAP is that the patient is admitted to hospital, more specifically into a stroke unit, and thus, the exposure to health-care-associated organisms is similar (57). However, studies have been conducted to analyse and describe the risk factors for SAP in different stroke units. For example, a study performed by Finlayson et al (59), described important risk factors that would increase the risk of SAP. Among these are: age, sex (male), a non-lacunar stroke, severity of stroke, dysphagia, COPD, pre-existing dependency and the presence of angina/coronary artery disease.

Comparing the three classifications of pneumonia, the common risk factors are increasing age, COPD/chronic bronchitis/respiratory condition and immunosuppression. Besides these, evidence suggests that SAP has risk factors of its own, since pre-existing cardiovascular disease, severity of stroke and a non-lacunar stroke were shown to increase the risk of SAP (60). As a result of these risk factors, various prediction tools have been developed and validated.

In 2006, Kwon et al published the pneumonia score, a prediction tool for patients who had suffered a stroke that would predict the probability of suffering pneumonia. This score involved 5 variables (40). Since then, other predictive tools were developed, among them PANTHER-IS (42), the A2DS2 score (44), the ISAN score (43) the Chumbler score (61), the AIS-APS score (38) and the ICH-APS score (39). All but PANTHERIS have common features among them, namely age, sex and severity on the NIHSS scores. The A2DS2 score, developed by Hoffman et al, reported atrial fibrillation as one of the predictor variables, which sets it apart from other prediction systems developed (44). The inclusion of atrial fibrillation as a risk factor was not discussed in previous evidence, but possible explanations for its association with SAP could include the association of AF with increased stroke severity (62, 63), which has been consistently associated with increased risk of SAP development. Further exploration between this association would be of interest to understand the increased risk.

It is important to note that these risk scores were derived retrospectively with the variables available in each of the studies and population cohorts at the time, which could lead to undue SAP variation due to the different endpoint definitions used.

Risk Score Predictor	Variables
Pneumonia score	NIHSS, Age, Sex, Mechanical Ventilation, Dysphagia
PANTHER-IS	Age, Glasgow Coma Scale, White Blood Cell count, Systolic Blood Pressure
A2DS2	Age, Atrial Fibrillation, Dysphagia, Sex, NIHSS
ISAN	Age, Sex, NIHSSS, modified Rankin Scale on admission, modified Rankin scale prestroke
AIS-APS	Age group, Medical history/comorbidity (atrial fibrillation, CHF, COPD, Current smoking), Prestroke dependence, Admission NIHSS score, GCS score, Dysphagia, OCSP subtype, glucose on admission
ICH-APS	Age group, Current smoking, excess alcohol consumption, COPD, Pre-stroke dependence, GCS score, NIHSS score, Dysphagia, Infratentorial location, extension into ventricle, hematoma volume
Chumbler	Age, abnormal swallowing test, NIHSS score, found down at symptom onset, past medical history of pneumonia.
PASS pneumonia predictors	Age, male sex, history of COPD, Pre-stroke disability, ICH, stroke severity, dysphagia

Table 1.2.3.1. Variables in the different predictor scores for SAP (CHF stands for congestive heart failure, COPD for Chronic Obstructive Pulmonary Disease, GCS for Glasgow Coma Scale, NIHSS for National Institutes of Health Stroke Scale, ICH for intracerebral haemorrhage)

As the table demonstrates, there are common predictors in the different predictor scores developed across the years. Age, sex, dysphagia and stroke severity are the most common score variables among the predictor scores, although dysphagia is not a component of the ISAN score. As such, these predictor scores are directly related to the already discussed risk factors. Stroke severity is mainly defined using the NIHSS in most scores, except on PANTHERIS, which uses the Glasgow Coma Scale. It is very important to note that these are risk predictor scores; they do not make any recommendations regarding treatment or management for patients with SAP, or state whether they have any validity in improving the outcomes of patients who have been diagnosed with SAP.

Since several score predictors have been developed, their validity is important, and several studies have been performed to determine this. For example, a systematic review done by Kishore et al compared 9 risk scores, and found that no single score excelled in comparison to another (36). As such, other studies aimed to test the validity of the scores within their own populations. An example of this validation was a study performed by Gong et al in 2016 (64), in which 3 predictor scores were compared: A2DS2, Chumbler's Score and AISAP. The main aim of the study was to see if these scores could accurately predict SAP in the Chinese population, and they found that all 3 had similar accuracy to predict SAP, with C-statistics of 0.728, 0.659 and 0.758 respectively. A further validation study conducted by Zapata-Arriaza et al in 2018 in Spain externally validated the ISAN, A2DS2 and AIS-APS scores in a prospective study. They found that A2DS2, AIS-APS and ISAN scores were reasonably accurate in predicting SAP in the Spanish population, with C statistic scores of 0.80, 0.82 and 0.83 for each respective score (65). Another study, performed by Cugy et al, compared the Pneumonia score, A2DS2 and ISAN score in a French population. Their findings are similar to Gong et al and Zapata-Arriaza's studies, in which all 3 scores, the A2DS2, AIS-APS and ISAN, had a similar accuracy in predicting SAP (66). However, there is an important limitation to Gong and Cugy's studies: both were single-centred and retrospective, making them limited in scope. Zapata-Arriaza's study, however, was prospective and multi-centre, and made the diagnosis of SAP according to the CDC criteria. Taking all of the information that is readily available and validated by research, the

ideal predictor score is one that is easy to use in a clinical setting, has a high discrimination and calibration score and informs management meaningfully. Some of the scores have certain limitations in a clinical setting, for example, the PANTHER-IS score uses the GCS, but in some patients with stroke that present with aphasia, the GCS is not the best tool because it affects the score and doesn't reflect the actual neurological deficit of the patient. The Chumbler score with the 'found down at symptom onset' is very dependent on the initial presentation of the patient, and in a clinical setting, the symptom onset needs to be clarified as either pneumonia symptoms or stroke symptoms. Both the AIS-APS and ICH-APS scores are very complete, yet, in a clinical setting for predicting SAP, they require a lot of information, and the A2DS2 and ISAN scores have less variables and have similar accuracy at predicting SAP as demonstrated by Zapata-Arriaza et al. Thus, the ideal predictor score would be the one with the highest discrimination score, and the one that clinicians feel more comfortable using in a clinical setting, taking all of the aforementioned variables into consideration.

1.2.4. Pathophysiology of SAP

The pathophysiology of SAP is multifactorial, and still not completely understood. Experimental and clinical studies have contributed to our understanding of different mechanisms in the pathophysiology of SAP. There are three very important processes in the pathophysiology of SAP. The first is an infectious substrate i.e. a reservoir of pathogenic bacteria in the oro/nasopharynx and upper GI tract plus contamination from the hospital environment. The second important process is a means for the infectious substrate to enter the lungs, which would be oropharyngeal aspiration, impaired cough responses, or both. The third process is transient immunosuppression, which increases host susceptibility to infectious challenge.

The oral reservoir of microbiological agents in stroke patients presents challenges to measure, because many microbiological agents inhabit the gingival crevices, thus will not be detected with routine oral swabs. Oral swabs of stroke patients have shown a multitude of microorganisms,

ranging from gram negatives and gram positives to anaerobic bacteria. A study done by Boaden et al showed that oral swabs in 75 stroke patients, revealed 103 bacterial phylotypes (67). The most common microorganism they found was *Streptococcus salivarius*, followed by *Streptococcus pneumoniae.* Of all the participants, 30% developed an infection, but no association or correlation studies were done to see if there was any link between the two findings. Although this study provides some information regarding the oral flora in patients with stroke, it is limited by a small sample size and restricted to a single centre.

Dysphagia plays a significant role in the pathophysiology of SAP. Patients who suffer strokes are at risk of developing dysphagia (68) and thus have a much higher chance of oropharyngeal aspiration into the lungs (69, 70). Dysphagia has been found to be common in the first three days of stroke onset, with a prevalence ranging from 29% up to 81% (71). Dysphagia in stroke patients usually improves after the first seven days, which could provide an explanation as to why the frequency of pneumonia is higher during the first week after stroke onset then subsequently. It's important to note that this range of prevalence varies depending on the tools used to determine whether a patient was dysphagic or not. With dysphagia, there is an association between the loss of protective reflexes of the respiratory tract and infections of the lower respiratory tract. For example, a study done by Bray et al (72), compared patients who were assessed for dysphagia within 4 hours and those that were assessed within 72 hours. The patients with longer times for dysphagia assessment had a much higher risk of developing SAP compared with patients with shorter times of dysphagia assessment. The associated delays in assessment by SLT specialists were associated with a higher prevalence of SAP. Among the possible mechanisms related to this could be early screening might reduce the risk of inappropriate administration of fluids or food and thus reduce the risk of aspiration, and thus reduce the risk of SAP development. Another study done by Eltringham et al, published in 2018, showed that stroke patients with dysphagia have an increased odds of developing SAP (Odds Ratio (OR) of 8.57 (95% CI 5.65-13)) (73).

Even though dysphagia and the frequency of SAP have an established association, not all patients who have dysphagia have evidence of aspiration, yet still present with SAP. Likewise, not all patients that develop SAP have evidence of oropharyngeal aspiration. This would suggest that there is more to SAP than just dysphagia and aspiration. Experimental models in animals have proposed "stroke-induced immunosuppression" (74). This theory has been proposed after studies have shown that several changes take place in the systemic immune system after a patient suffers a stroke. These changes can be seen in both the innate and adaptive components of the immune system. Changes of the adaptive response include impaired early lymphocyte responses and reduced interferon gamma (INF-γ) production by natural killer and T cells (74). Changes in the innate immune response include elevated levels of Interleukin 1 and 6, as well as phenotypic changes to myeloid cell subsets and functional impairment of monocytes and neutrophils (75). Other preclinical models and clinical studies have shown that further changes can occur during a stroke, such as an activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. Glucocorticoids and cathecolamines are secreted as a consequence of the activation of these two systems, and both these substances are known to have a peripheral immunomodulatory effect (76). All of these responses have been shown to have effects on the innate and adaptive response of the immune system.

It has been theorized that pre-existing infection could contribute to SAP, adding to the burden of an already immunosuppressed patient with broncho-aspiration issues. Observational studies have suggested that chest infection is present in 20% of patients prior to stroke, which suggests that these patients already have community acquired microorganisms (77, 78). The stress the stroke induces in the patient could progress the chest infection of the patient, developing into SAP in conjunction with the aforementioned pathophysiological mechanisms. Hannawi et al summarize the pathophysiology of SAP, with a combination of both hypotheses of how SAP occurs in patients (76).
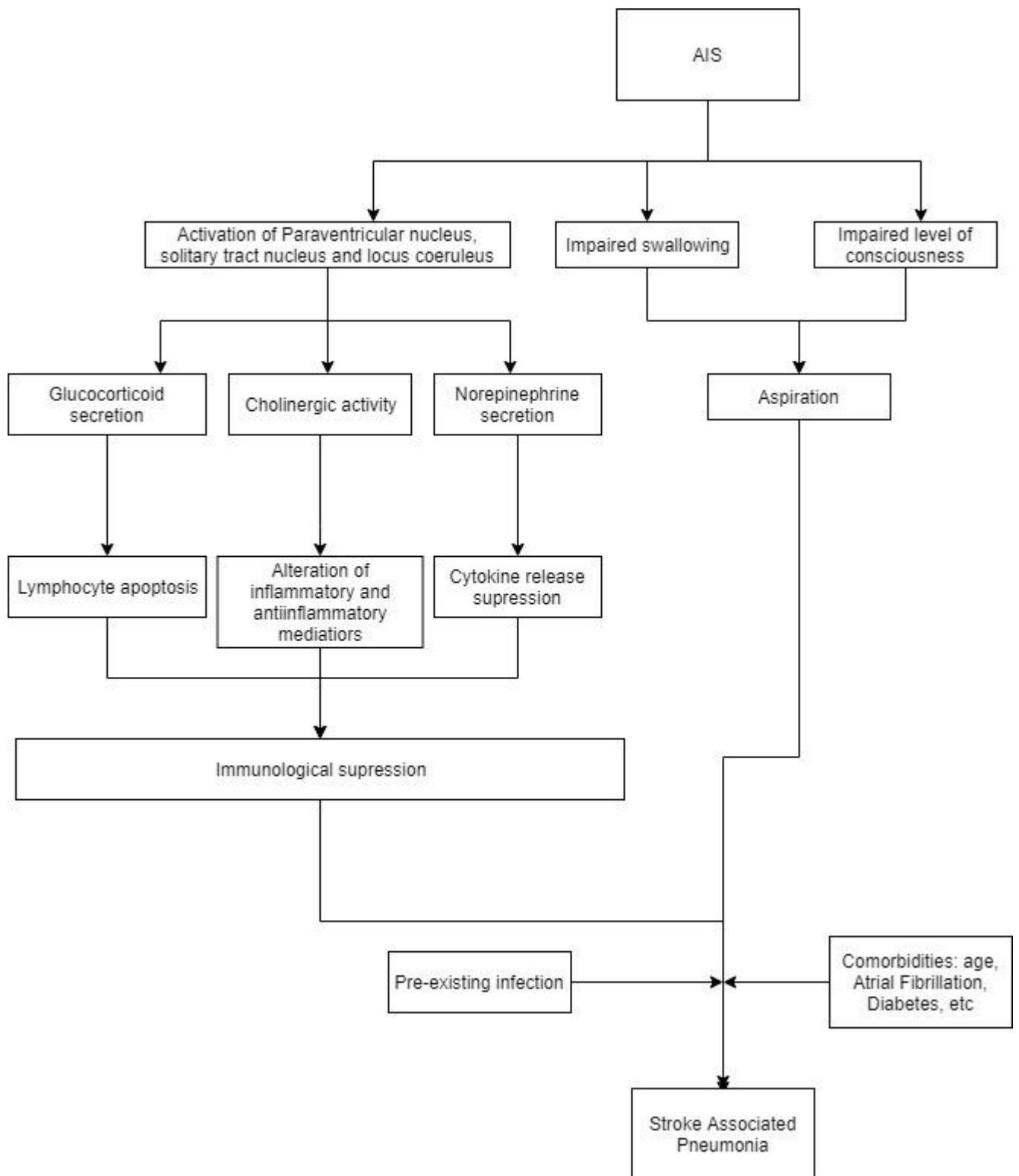
Figure 1.2.4.1. Summary of the pathophysiology of SAP, taken from Hannawi et al

1.2.5. Microbiology

The most common cause of pneumonia worldwide is *Streptococcus pneumoniae*, with an estimated frequency ranging from 11.9% to 68.3% in Europe (79, 80) and an estimated frequency of 10-15% in the United States (81). This frequency varies across the world, partly due to the application of the pneumococcal vaccine in the United States compared to Europe (82, 83). *S. pneumoniae* is the most common organism because it is the most common causative agent in CAP (84). For HAP, the most common microorganisms are gram negative bacteria, such as *Pseudomonas aeruginosa, Klebisella pneumoniae* and *Acinetobacter spp* (32, 85). With the traditional view that SAP is largely HAP, it might be expected that the microorganisms associated with SAP would be gram negative bacteria. However evidence provided in a systematic review performed by Kishore et al in 2018, showed that the most frequent microorganism in SAP was *Staphylococcus aureus,* followed by gram negative bacteria such as *K. pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenza, A. baumanii* and *Enterobacter cloacae* (86). Gram negative bacteria are more frequent, yet the fact that *Staphylococcus aureus* is the most common pathogen would suggest that there is a close relationship with healthcare practices, as it is a very common nosocomial pathogen (87). Although these data are important in determining the microorganisms associated with SAP, it's worth noting that good quality and reliable sputum culture are limited in patients with stroke and is limited to standard culture techniques. Another important limitation of the analysis is the inclusion of studies that were not designed to identify microbiological agents. Another limitation to highlight is the timing of sampling after stroke admission, which could lead to sampling bias. If the sampling took place in the first 24 to 48 hours, community organisms would likely dominate, whereas if the sampling took place in day 4, nosocomial organisms would be more likely to dominate. This phenomenon can be seen in Westendorp et al's study of 2011 (45), where they found that most of the microorganisms recorded in their meta-analysis in suspected SAP were nosocomial agents, which could suggest sampling bias.
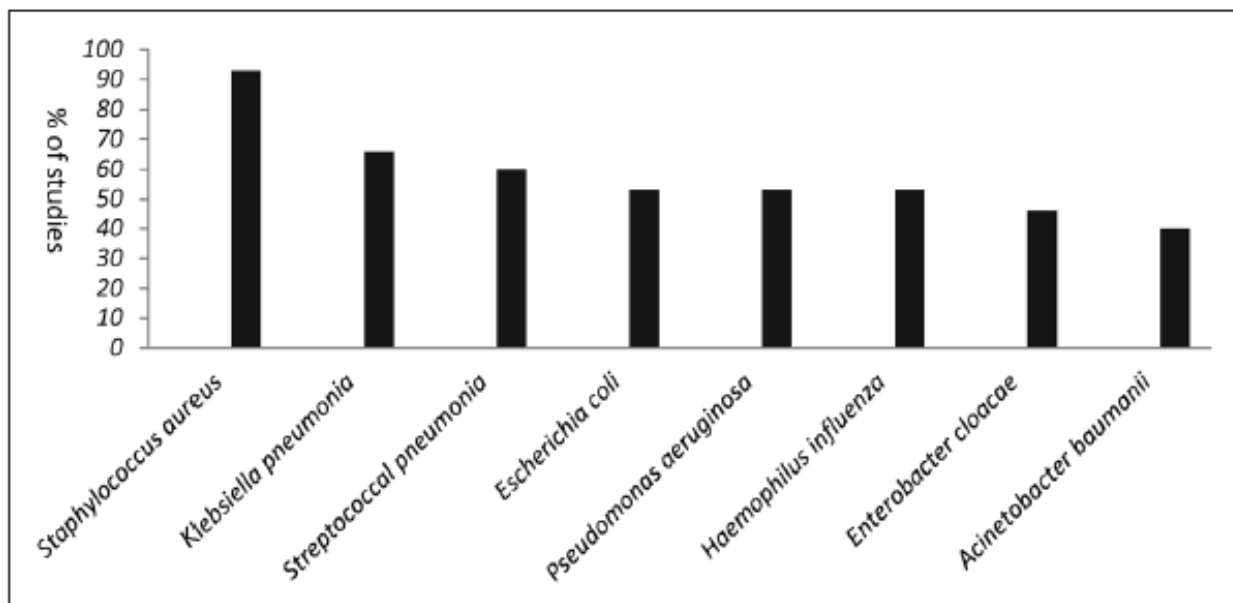
Figure 1.2.5.1. Figure showing the percentage of studies with the most common microorganisms. Taken from Kishore et al.

1.2.6. Prevention and management of SAP

There are currently very few effective strategies for preventing SAP in clinical practice. Most of these recommendations come from limited studies, and thus the levels of evidence are not high enough to warrant use in clinical practice. The NICE guidelines for stroke rehabilitation focus on swallowing, with a small suggestion to: "have an effective mouth care, to decrease the risk of aspiration pneumonia" (25). There is little to no information regarding the actual complication of pneumonia, with no direction for which criteria to use to diagnose pneumonia or how to treat it. The same could be said for the Scotland Intercollegiate Guidelines Network (SIGN) guidelines. Compared to the NICE guidelines, SIGN guidelines expand more on dysphagia therapy, in which they state various approaches for improving patient outcomes, such as muscle-strengthening exercises, electrical stimulation or biofeedback to improve the patient's dysphagia. However, with regards to the complications of dysphagia, there is only a passing mention of the risk of pneumonia. As such, there is a lack of protocol and standardization regarding SAP, and this could lead to various issues regarding the diagnosis, prevention and treatment of such an important complication of stroke.

Available guidelines provide little information regarding the prevention of SAP and as such, clinical trials have been conducted to investigate different approaches in reducing the incidence of SAP. For example, SAP being an infectious condition, various trials approached the issue using preventative (prophylactic) antibiotics. The STROKE-INF trial published in 2015 using randomised stroke patients with dysphagia to prophylactic antibiotics vs standard care alone what were the controls showed that were no significant differences in the mortality or functional outcomes between the treatment groups (adjusted OR of 1.21 [95% CI 0.71-2.08]) (88). Another clinical trial, the PASS trial, looked at prophylactic intravenous ceftriaxone vs usual care and improved functional outcomes in 3 months in unselected patients, and they concluded that prophylactic IV antibiotics have the same effect on functional outcomes compared to standard care patients (OR of 0.94 [95% CI 0.82-1.09]) (89). Both studies had several limitations and, in the case of the PASS trial, had a smaller sample size than intended due to a lack of funding, which led to changes in methodology analysis. Kalra et al's study focused on stroke unit recruitment, which led to a smaller population than intended. However, whilst these are important limitations, they provide some insight into the use of prophylactic antibiotics for SAP, which could be ineffective. However, better selection of at risk patients, different antibiotics and earlier treatment could help confirm this finding. To complement these trials, a Cochrane review published in 2018 further studied these findings in a systematic review and meta-analysis of 8 studies, which included Kalra et al and Westendorp et al's studies. They found no association between preventive antibiotic therapy and the occurrence of pneumonia in ischaemic or haemorrhagic stroke patients (90).

Given the lack of evidence for preventive antibiotics, other pharmacological agents have been evaluated to see if they reduced the risk of SAP. Examples of these were the gastroenterological agents proton pump-inhibitors and H2 antagonists. Observational retrospective studies undertaken by Ho et al and Arai et al (91, 92) have shown that patients who received anti-acid treatment, either by PPIs or H2A, were associated with an increased risk of having pneumonia with a hazard ratio of 1.44 [95% CI 1.18 to 1.75] and relative risk of 2.0 [95% CI 1.12 to 3.57] respectively. These data align

with the information available for CAP and HAP regarding these medications, which suggests that

PPIs and H2A increase the risk of pneumonia (93). In contrast to antibiotics, PPIs and H2A, there are

pharmacological interventions that have some evidence that they may reduce the risk of SAP, with

one example being the anti-platelet agent cilostazol. Cilostazol was associated with reduced risk of

SAP development in a retrospective study conducted by Nakamura et al in 2018, and was associated

with a decreased risk of pneumonia with a Hazard ratio of 0.32 (0.11-0.86 95% CI) (94). The same

possible benefit can be seen in stroke patients with chronic sequelae as a study performed by

Shinohara et al in 2006 lower incidence of pneumonia compared to placebo across patients with

stroke after a three-year follow-up (95). However, there are important limitations in both of these

studies, with Nakamura et al's study recruiting a very small number of patients (n=199) and

conducted in a single centre, which limits the generalizability of their findings. Shinohara et al's

study was an analysis of clinical trial data from 1992 to 1996 and used individual clinician decision for

the definition of pneumonia, which could lead to possible inaccurate diagnosis and bias of the study.

Similar possible protective benefits can be seen with ACE inhibitors. A study done by Okaishi et al in

1999 found that elderly patients with ACEI had a lower risk of aspiration pneumonia, one of the main

pathophysiological mechanisms of SAP (96). However, it is important to clarify that these findings

were not in acute stroke, it was in a case-control study with a follow up period of 1 year in stroke

survivors. Shinohara et al's 2012 meta-analysis adds evidence for possible benefit. They reported

that patients who were on ACEI compared to controls had a relative risk of 0.61 [95% CI 0.51-0.75]

(97) in prospective cohort studies. It is very important to note that these studies have various

methodological issues and were not randomised clinical trials. Other possible beneficial agents, such

as metoclopramide, have shown promise in preventing SAP in dysphagic stroke patients. An RCT

undertaken by Warusevitane et al in 2014 (98) showed that metoclopramide vs placebo in a 21 day

follow up period showed some potential benefits in stroke patients, specifically in those receiving

nasogastric feeding. The mean number of episodes of pneumonia in the placebo group was 1.33 and

the mean number of episodes of pneumonia in the metoclopramide group was 0.27, with a rate

ratio of 5.24 [95% CI 2.43 – 11.27], showing a possible benefit for its addition to the nasogastric feeding process of care. However, this was a small-scale study, with only 60 participants in a single centre, and a larger multicentre study is funded and due to commence in the UK (MAPS-2).

Other non-pharmacological approaches to SAP prevention have been investigated. One example undertaken by Kulnik et al, investigated whether respiratory muscle training could improve voluntary cough as a measure of reducing the incidence of SAP (99). They looked at 3 groups, respiratory training for maximal inspiratory peak flow, respiratory training for maximal expiratory peak flow and a control group undergoing sham training. They showed that respiratory muscle training improved mean maximal inspiratory and mean maximal expiratory flow; however, there were no differences between all three groups in the rate of pneumonia at a 3 month follow up. It's very important to note that there are significant differences between the definition used by PICSES and Kulnik et al's definition of SAP. Their time window for the definition of SAP was extended to 28 days, which is not in line with PISCES's definition. In their published results, they also focused on rates of pneumonia at 3 month follow-up, limiting the information available for potential SAP patients (100).

Another non-pharmacological intervention investigated was one conducted by Cuesy et al in Mexico. They approached the issue using a manual turning and mobilisation (turn-mob) intervention. They used this program to see if they could reduce the incidence of nosocomial pneumonia in stroke patients using this manual manoeuvre, and found a reduction in the incidence of SAP (101). However, the lack of information on the mortality or outcomes of these patients is something to take into consideration, as it is not clear whether receiving this therapy resulted in any improvement in outcomes. Nevertheless, it does support the guideline recommendations detailed above, which state that mobilisation is key in improving outcomes in stroke patients. Other non-pharmacological manoeuvres that were researched include the positioning of a stroke patient, explored in the international multi-centre study of Anderson et al (102), in which they investigated whether the

supine positioning of a patient in acute treatment of stroke would improve outcomes compared to patients in a seated position. Although the supine position group had lower frequency of pneumonia, the difference between this group and the control group was not significant, with a reported OR of 1.01 (0.92 – 1.10 95% CI). Though this conclusion means no effect on SAP prevention, it merits careful consideration, as most patients included had mild neurologic deficits, which would limit its potential use on more severe stroke patients, the principal population suffering from SAP. This was also represented in the lower-than-average incidence of SAP in the study population, which can also limit the conclusions made from such a study. It would need to be trialled in a less select population in order to see its effects on SAP patients.

Another interesting strategy taken to prevent SAP is oral hygiene. This was investigated in three studies, published by Gosney et al in 2006 (103), Wagner et al in 2015 (104) and Yuan et al in 2020 (105). There was an association between lower risk of SAP and the different approaches to oral hygiene, with Gosney et al using an SDD (selective oral decontamination of the digestive tract) gel vs placebo and Wagner et al using oral antiseptics. The other main difference is that Gosney's study was an RCT, while Wagner's study was a before and after implementation study, which could increase the confounding factors for their conclusions. Gosney's study does not report an OR or Hazard Ratio (HR), while Wagner's study showed an OR of 0.71 [95% CI 0.51-0.98], demonstrating a decreased risk of SAP with oral healthcare. Yuan et al's study was a single centre pilot RCT done in China compared intensified oral hygiene care (IOHC) to standard practice in the first 7 days of admission from stroke to determine whether this new approach reduced the incidence of SAP. Their findings suggest that in patients with lower GCS scores this approach seems to be effective with an OR of 0.150 [0.029 to 0.766]. However, there are important limitations to their findings. Their study used the definition of probable SAP proposed by the PISCES group instead of the definition of definite SAP (37), which could lead to possible overestimation of the effect of their findings, because pneumonia is not confirmed using chest x-ray. Another important limitation is the small sample size

they studied (n=84), which could also limit their findings. However, this is encouraging evidence, as it

could lead to further studies that could reduce the incidence of SAP.

PREVENTION STRATEGY	STUDY DESIGN AND SAMPLE SIZE	SAMPLE SIZE	NO EFFECT/POSSIBLE HARM/POSSIBLE BENEFIT
ANTIBIOTICS/CEFTRIAXONE (88, 89)	Kalra et al – RCT	(n=1224)	No effect
	Westendorp et al – RCT	(n=2550)	No effect
PROTON PUMP INHIBITORS (91, 92)	Ho et al - observational study	(n=7965)	Possible Harm
	Arai et al – observational study	(n=3582)	Possible Harm
H2 ANTAGONISTS (92)	Arai et al – observational study	(n=3582)	Possible Harm
CILOSTAZOL (94, 95)	Nakamura et al – observational study	(n=199)	Possible benefit
	Shinohara et al – pooled analysis	(n=1064)	Possible benefit
ACE INHIBITORS (97)	Shinohara et al – meta-analysis (n=8693)	(n=8693)	Possible benefit
VOLUNTARY COUGH (99)	Kulnik et al – RCT	(n=82)	Not enough data
TURN-MOB (101)	Cuesy et al – RCT	(n=223)	Possible benefit

METOCLOPRAMIDE (106)	Warusevitane et al – RCT	(n=60)	Possible benefit
SUPINE POSITIONING (102)	Anderson et al – RCT	(n=11093)	No effect
ORAL HEALTHCARE (103-105)	Gosney et al – RCT	(n=203)	Possible benefit
	Wagner et al – before and after implementation study	(n=1656)	Possible benefit
	Yuan et al – RCT	(n=84)	Possible benefit

Table 1.2.6.1. Prevention strategies for SAP

1.2.7. Treatment

SAP is treated with antibiotics. However, as mentioned above, there has been no standardization or evidence-based guideline on the diagnosis or treatment options regarding antibiotic therapy for SAP, until a consensus recommendation from the PISCES group in 2019 (107). A previous study from Germany published in 2012 showed that clinicians treated SAP using multiple antibiotics, based on the guidelines for HAP treatment in Germany (108). They used primarily narrow-spectrum antibiotics such as cephalosporins, aminopenicillins, fluoroquinolones in the first 4 days of diagnosis and broad spectrum antibiotics in late stage onset HAP (32). However, this study was cross-sectional and does not provide data about the outcomes of patients who received this type of therapy. Furthermore, it does not take into account the concept of antibiotic-resistant bacteria, which complicates the outcomes of patients suffering from SAP. A study done by Yan et al, published in 2014, showed that elderly patients who developed SAP had *E. coli, P. aeruginosa* and *K. pneumoniae* showing resistant to ceftriaxone, aztreonam, ticarcilin and imepenem, providing some evidence that antibiotic therapy

needs further study to improve the outcomes of patients with SAP. This study, however, is limited in scope, as it only takes into account one centre, and depends on the collection of sputum of patients who were hospitalized, which could lead to sampling errors (33).

SAP treatment recommendations have been proposed by the PISCES group (107). Their review and recommendations were given on the basis of a literature review and expert consensus. Their recommendations are summarized into the following categories: definite onset preceding stroke, SAP and pneumonia >7 days from stroke onset. For the first and final categories, their recommendations are to follow CAP and HAP guideline treatment recommendations respectively. For SAP, their recommendations are divided into two categories. The first is SAP <72 hours (Early SAP), and the latter between 72 hours and 7 days (Late SAP). For early SAP, empirical antibiotics are recommended to include Gram-positive cocci and *H. influenza* coverage. Late SAP empirical antibiotics include Gram positive cocci coverage, as well as coliforms with or without *Pseudomonas spp.* coverage. It is important to note that there is no evidence that these recommendations are effective in improving the outcomes of patients with SAP, however there is evidence to suggest that some antibiotics might improve the outcomes of SAP patients. An individual patient data pooled analysis from the VISTA Acute dataset, (109), reported that patients who received macrolides such as clarithromycin had better outcomes, e.g. OR of 0.59 (95% CI 0.42 – 0.83) for modified Rankin Scale, an OR of 0.50 (95% CI 0.35 – 0.72) for the Barthel Index and an OR of 0.67 (95% CI 0.56-0.80) for the NIHSS score at 90 days. While this is promising evidence, there are several considerations to take in to account when interpreting these results. The first is the size of the cohort of patients who received macrolides compared to other antibiotics. The macrolide cohort consisted of 142 patients (5.24%), the smallest of the entire sample, compared to, for example, the cohort of fluoroquinolones [930], cephalosporins [815] and Penicillins plus β-lactamase inhibitors [873]. This difference in sample size could affect the precision the results. Another important consideration is the profile of the macrolide coverage. Macrolides are usually used in relatively stable patients compared to other antibiotics (110), as the patient is not necessarily admitted into the hospital ward where the risk

factors for nosocomial infection are high. This could bias the type of patient that is prescribed a macrolide, as usually cephalosporins, fluoroquinolones and other antibiotics are used in more critical patients. Further research is still needed to identify whether addition of macrolides could improve outcomes in SAP patients, ideally in the form of a randomized controlled trial.
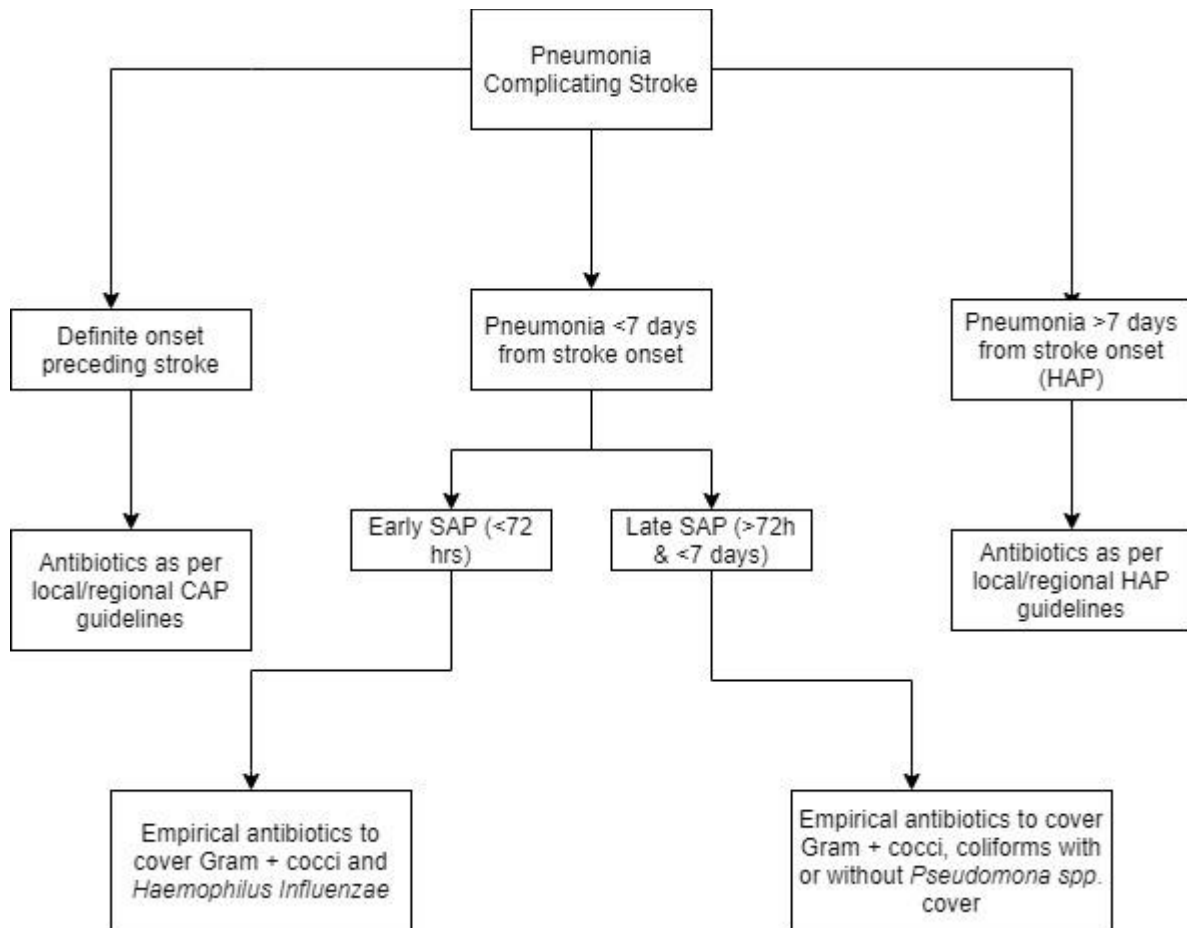
Figure 1.2.7.1. Flow chart summarising the approach to antibiotic treatment of SAP, HAP and CAP. Taken from the PISCES group recommendations (REF)

The issue of antibiotic resistance is consistently raised and must be addressed. According to the WHO, antibiotic resistance/antimicrobial resistance defined as microorganisms (such as bacteria, fungi, viruses and parasites) change after exposure to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials and antihelmintics). As a result, these medicines become ineffective and infections persist in the body, increasing the risk of spread to others (111). The use of antibiotics in SAP is of paramount importance, as they are the go-to treatment for infection.

However, global use of antibiotics increased 65% from the year 2000 to the year 2015. This translates from 21.1 billion defined daily doses to 34.8 billion daily doses (112). This increase has an effect; with increased use comes increased antimicrobial resistance. Antibiotic stewardship is of principal importance, and thus, a lack of protocol and standardization on SAP treatment could be translated into an increased antimicrobial resistance, and with increased antimicrobial resistance, the outcomes of patients with SAP could be affected.

1.2.8. Implications of SAP

As a complication of stroke in hospitalized patients, SAP has various consequences on patient outcomes. Among the most important consequences to note is that SAP has been independently associated with increased mortality, worse functional outcomes, increased healthcare costs and increased length of stay. Patients diagnosed with SAP had a Neurology Intensive Care Unit (NICU) stay 6 days longer than patients who were not diagnosed with SAP (34). Other researchers have published similar findings, for example Katzan et al, in 2003, found that patients with pneumonia after stroke had over six-times increased mortality, with a Relative risk (RR) of 5.9 [95% CI 5.1-6.8] (113). It is important to note that investigators mention that the deaths occurring within the first 3 days of hospitalization are more likely to be due to the direct effect of neurologic event rather than pneumonia. As such, this RR could be biased and must be studied carefully. Koennecke et al in 2011 demonstrated that patients diagnosed with pneumonia during their hospital stay after a stroke had a mortality risk of 5.39 [95% CI 2.98-9.75], and a poor outcome rate increase of nearly 25 times those without. It is important to note that there is a very small group of severe stroke patients, which could influence the results and confidence intervals of the study (114). Teh et al, in 2018, found that patients who had SAP had an increased 30 day mortality, a worse functional outcome and higher odds of an increased length of stay, compared to patients who were not diagnosed with SAP (41). Another important implication is the healthcare cost associated with the increased morbidity associated with SAP. For example, Ali et al showed that SAP increased acute care costs for stroke by approximately 80% (115), which shows the health economic burden.

Taking all of the evidence provided into account, it can be concluded that patients diagnosed with SAP will have much poorer outcomes and a higher mortality rate than patients not diagnosed with SAP. Therefore, the implications of poorer outcomes will not only impact the patients themselves, but also the healthcare system.

1.3. Sentinel Stroke National Audit Programme (SSNAP) and Registries

With stroke and SAP having such an important impact on the population, several countries have taken action to manage and improve stroke-related healthcare. Registries have been created in several countries, as both a means to collect data about the characteristics of people with stroke and to monitor different core processes and clinical outcomes in stroke (116, 117). In the UK, the Sentinel Stroke National Audit Programme (SSNAP), is a registry based in Kings College London that gathers information on all patients with confirmed stroke admitted to hospital in England, Northern Ireland and Wales (47).

SSNAP is dedicated to measuring two important aspects of stroke: the processes of care provided to stroke patients and the structure of stroke units compared to the NICE guidelines. The processes of care measured in clinical audit focus on four important aspects: hyperacute and acute care, recovery, rehabilitation and six-month outcome. The clinical audit has several aims, which are: to monitor and measure the services of stroke units across the UK, to monitor the progress of different organizational changes made to stroke unit services against different quality criteria used in the NHS, to aid and support clinicians in identifying where improvements are needed and to serve as platform for lobbying and change in stroke care across the UK, for both clinicians and patients. This audit reports the information divided into 4 different datasets: national, regional, Clinical Commissioning Group and geographical (47). In this way, the information gathered can be divided and analysed with different approaches, and as such, can give a much broader picture of the clinical aspects of stroke demographics and care in the UK. Another important key feature of SSNAP is that it is mandatory at site-level across all units admitting stroke patients. This way, there is a constant flow of new

information for policy and decision making, as well as research and the other uses stated in SSNAP, such as health economics and quality improvement.

A key aspect of a clinical audit is that only 'locked' data is available for analysis. In this case, 'locked' means data that has been signed off by a lead clinician. This includes data for the first 72 hours, discharged patients and six-month follow-up. Another key facet is the way the data are divided into 'patient-centred' and 'team-centred' results. This way it is possible to analyse the two main components of outcomes in stroke care: the patient pathway and the team pathway. The clinical audit also takes into account the different stroke services available to patients, and divides them into five different categories: routinely admitting acute teams, non-routinely admitting acute teams, non-acute inpatient teams, post-acute non-inpatient teams and six-month assessment providers (47).

There are certain criteria that need to be met before patient data are entered into the SSNAP dataset, for both patients and stroke services alike. Patients need to have a diagnosis of stroke coded as I-61, I-63 or I-64 according to the International Statistical Classification of Diseases and Related Health Problems (ICD) and should be over 16 years of age. Stroke services that treat at least 10 patients per year are eligible to submit data to SSNAP. Data are provided by the SSNAP team every three months for inpatient teams, and every four months for non-inpatient teams (47).

There are two further audits in SSNAP: the SSNAP Acute Organisational Audit and the SSNAP Post-Acute Organisational Audit. The SSNAP Acute Organisational Audit is a biennial report of the quality of stoke service organisation in acute settings (118). Among the aspects audited are staffing levels, acute care processes, TIA services, access to specialist support and communication with patients and carers. The SSNAP Post-Acute Organisational Audit collects data and information pertaining to the post-acute stroke services and includes the different stroke units and several factors such as the availability of swallow screened trained nurses; access to multidisciplinary care provision; and 7 day working standards.

Data provided by SSNAP are claimed to be of a very high quality by the Royal College of Physicians and are consistently systematically retrieved and clinically appraised, making it a very solid foundation for audit, research and guideline material. A clear example of the uses of these high quality data is that they are used to develop the NICE guidelines for stroke, and are aligned with the measures for Cardiovascular Disease Outcomes Strategy (53). This is a national strategy issued by the department of health of the UK government to reduce cardiovascular mortality in the UK (119).

Another way that SSNAP ensures high quality data is by using the 44 defined indicators of high quality stroke care. These were chosen by the Intercollegiate Stroke Working Party (ICSWP), a group of senior representatives from all professional bodies involved in stroke care (120). The main key indicators stated by the ICSWP are the following: 1) Scanning, 2) Stroke unit, 3) Thrombolysis, 4) Specialist assessment 5) Occupational therapy, 6) Physiotherapy 7) Speech and language therapy 8) Multidisciplinary team (MDT) working, 9) standards by discharge and 10) Discharge processes. Each of these indicators has sub-indicators, as are shown in the table in the appendix taken from the SSNAP webpage

SSNAP data, beside the audits and uses that it poses, also has three further proposed uses. The first is quality improvement, which it proposes to be a platform to initiate quality improvement projects at various levels. This process involves various steps: 1) using theory and data to develop a way to solve a problem and improve clinical care, 2) Using systematic process to test and implement change and 3) measuring the size of the improvement/change. With these data and other measures, clinical care can improve and thus, stroke outcomes can be improved. Another further use mentioned is the development of a health economics research project developed with NHS England to estimate the costs of stroke care. Data from SSNAP can be used to estimate health and social care cost, which can lead to potential local cost-saving measures. The third and final further use is research. SSNAP provides the biggest and most complete data bank of stroke patients in the UK, making it a very useful tool in medical research (121). Various studies have used SSNAP data for research, such as the

development of ISAN by Smith et al (43) or studies investigating swallow assessments delays and

SAP association or association between stroke nurse work intensity and stroke clinical outcomes (72, 122). The basis for the research in this thesis was data provided by SSNAP regarding the prevalence of SAP in England and Wales.

With all of the implications and uses that SSNAP can offer to researchers, it is very important to note the diagnosis of SAP is not standardized, as mentioned beforehand. SAP is recorded in SSNAP as antibiotics for new chest infection/pneumonia within first seven days of admission. It does not capture data regarding methods of diagnosis, antibiotic use, lab variables, chest x-ray use, etc. All of the implications mentioned beforehand, as well as SSNAP's characteristics, show that there is a need for standardization on the diagnosis of SAP.

1.4 Project description

The variation in frequencies of SAP in stroke units can be seen in three different settings. 1) between different studies, 2) between registries and 3) within registries. The variation between different studies can be seen clearly in Kishore et al's publication of 2015 (35), in which some studies present a frequency of 5.2% while others present a frequency of 56.8%. The studies presented have different criteria for the diagnosis of SAP, from the CDC criteria and Mann's criteria to the ASTIDS criteria, and this could account for some of the variability. However, with such a difference in variation, the question of clinician diagnosis is clearly one to consider. To illustrate the point, Kalra et al in 2016 published a study comparing algorithm based diagnosis vs clinician diagnosis in the same population. They showed that clinicians had a higher chance of having false-positives compared to the algorithm based diagnostic approach. This means that clinicians, in this study, could possibly have been overdiagnosing patients with SAP, which could lead to an increased variation of SAP (123). Registries, as explained earlier, include much larger populations than research cohorts. However, Kishore et al in 2016 (36) found that the variation of the frequency of SAP is still prevalent across registries. For example, in this study, the SSNAP registry reported a frequency of 6.7%, and the CNSR 11.4%. This

could be attributed to patient population characteristics, but it is important to note that both

registries have different methods of recording SAP, with SSNAP being clinician reported, while the

CNSR uses the CDC criteria. This could explain some of the variation, but further study and

comparison would be needed between these two registries. Thirdly, variation can be seen within

registries, and Bray et al 2016 highlighted this in a preliminary, study using SSNAP. The main aim was

to describe the variation in the frequency of SAP across all hospitals in England and Wales, using

predictive models and comparing them to observed models. The frequency in predicted models

ranged from 7 to 13%, while the observed frequency went from below 1% to 24% (124). Whilst this

unpublished preliminary study identified variation in observed SAP prevalence across stroke units in

England and Wales, it did not explore potential explanations for this variation or potential relevance

to clinical practice. Such variation could represent under- or overprescribing of SAP in different units

and have implications for both antibiotic stewardship and clinical outcomes of patients. Further

study could identify potential targets for interventions to reduce the variation in SAP, improve

antibiotic stewardship and individual and unit level outcomes.

1.5 Aims and objectives of the project

The main aim of the project is to investigate the variation of SAP prevalence across different UK

stroke units, what factors are associated with the development of SAP and then investigate the

extent of SAP impact on clinical outcomes. To achieve this aim, several objectives were addressed.

The first was to describe the variation of observed SAP across England and Wales and to investigate

how clinical characteristics influence this variation. The second objective was to investigate how

stroke care processes and their timing are associated with SAP development. The third objective was

to investigate the different clinical factors and investigations, and their thresholds, used by clinicians

to initiate antibiotics for SAP. The final objective was to establish the relationships between SAP and

clinical outcomes in England and Wales.

1.5.1 Project overview

The above objectives were addressed using two different approaches. The first was analysis of a dataset from SSNAP comprising patient level data. These analyses will be discussed in the following chapter. The second approach involved a decision-based cross-sectional questionnaire that was distributed to clinicians of various grades and regions to determine the main clinical factors and investigations, and their thresholds, that prompt clinicians to initiate antibiotics in suspected SAP.

1.5.1 Project overview

Chapter 2 - Methods

2.1 Introduction

In this chapter, I describe the objectives for the methodology of the project, including the statistical analysis plan and survey methodology.

2.2 Data source

This thesis used patient level variables from SSNAP. The criteria to be included in the thesis were all confirmed strokes in England and Wales admitted to a HASU or ASU from the 1st of April 2013 to the 31st of December 2018.

2.2.1 Regulatory approval and data transfer

SSNAP forms part of a network of clinical audits called the National Clinical Audit Programme [NCAPOP] that fall under the regulation of the Healthcare Quality Improvement Partnership [HQIP](125). Among the programmes that fall under the NCAPOP and HQIP umbrella include SSNAP, the National Adult Diabetes Audit, the Falls and Fragility Fracture Audit and the Heart: National Heart Failure Audit. HQIP was formed in 2008 to promote quality in healthcare, and to increase the impact of clinical audits on healthcare improvement quality (126).

With SSNAP being under the supervision of HQIP, all data requests need to go through HQIP. The process of requesting data from the audit programme involves several important steps. The first step taken in my PhD project was to determine which variables would be extracted from the dataset. The variables were chosen to determine the variation and all recorded variables that could affect the frequency of SAP across all stroke units, from clinical characteristics to healthcare processes.

After the data variables have been selected, data governance is the next step. Data can be divided into three different categories: anonymized data, limited access de-identified data and personal data. Each category has different restrictions on its uses in research, and each one has different materials and evidence that need to be presented for the data to be released. For example, for limited access de-identified data, among the evidence that must be presented is the NHS data

security and protection (DSPT) toolkit (127). This toolkit is an online instrument that enables

institutions to demonstrate that they comply with the data governance measures required by UK law

in order to manage patient data. The University of Manchester currently is enrolled with the DSPT

toolkit with its own identifier, called an ODS number, which can be found online.

After all of the data governance issues have been dealt with, the applicant must complete a Data

Access Request Form (DARF). This document has a total of 23 sections, some of which are obligatory

and others only need to be filled out if one is requesting personal data. For my application, I had to

fill in 22 sections of the document, as can be seen in the appendices below. Among the evidence

that needed to be presented on behalf of the applicant are the table of variables, the ethics

approval/evidence that ethics is not needed, a data flow map, data governance evidence and fair

processing information by the applicant. The data provider, SSNAP, had to present the statement of

ICO limited access safeguard and Fair processing information. A draft version before approval can be

found in the appendices.

After all evidence had been gathered, the DARF had to be presented to the Data Access Request

Group (DARG) for revision. Said revisions take place once a month and DARG review all DARF

requests from all of the audits that come under the umbrella of NCAPOP. Once the reviewing

committee has made a decision, the applicant is informed with several possible outcomes, the first

being that the application has been successful, the second that amendments need to be made and

to submit a re-application, and the last being a rejection from DARG. Data protection is a very

serious issue in the UK, and this data request process is just one example of how seriously data

needs to be handled.

Regarding the DARF for this project, it took three attempts to get approval from HQIP (final approval

form in appendix). HQIP approval was granted in August, after extensive review by the DARG

committee. After their approval, the next steps were to make sure all the different safeguards were

in place for the data transfer at the University of Manchester. The 2 main steps needed for this are

the development of a data management plan and data storage access request. The data

management plan is a questionnaire and document that is stored on a server, to which only the

research team has editorial access, but is open for all who have a university account to view. After

the development of this plan, data storage access can be solicited to the IT team of the University of

Manchester. Data stored in this server complies with all the data research policies of the University,

and, as such, also complies with all the safeguards that HQIP demands (128).

After the initial data transfer request was approved, subsequent amendment and extension requests

had to be submitted in July of 2020 and July 2021 respectively. In the amendment we submitted in

2020, we requested additional information on the NIHSS score, by asking the score of each individual

component of the NIHSS score. We did this to ensure there was no misclassification in the NIHSS

score that could lead to misleading implications on stroke severity. In July 2021, asked for the

extension as HQIP policy changed in 2020, stating that data access requests were only allowed for

one year, and any following years of maintaining the dataset needed to be approved by HQIP.

For the survey section of our study, ethical approval was deemed as not needed. The ethics

committee of the Division of Cardiovascular Sciences at the University of Manchester was

approached and was presented the study in question. After deliberation, it was deemed that ethical

approval was not needed because it was anonymous and asking questions in their professional

competency.

2.3 Statistical Analysis Plan

2.3.1 Main aim of statistical analysis
The overall aim of the statistical analysis was to investigate factors associated with the variation of

SAP across stroke units in England and Wales, investigate the association of stroke care processes

and the development of SAP, and the relationship between SAP and clinical outcomes.

2.3.2 Study population

The dataset comprised of all confirmed strokes registered in SSNAP from the 1st of April 2013 to the 31st of December of 2018 in England and Wales. It's important to note that SSNAP is an ongoing clinical audit, with participation of all admitting hospitals in England, Wales and Northern Ireland. All data that was used for this project was observational. The case ascertainment for SSNAP is an estimated 95% (118). For the objectives of the study, a *post-hoc* decision was made to focus on specialist stroke unit. This was done to focus on specialist stroke units and not those that had been repurposed for the occasional stroke patient, which would be a more accurate representation of stroke unit care across England and Wales and to reduce any skewness in our data.

After the amendment approval by HQIP, the dataset comprised of 458,829 patients across 328 stroke units in the same five year period. This increase of 2239 patients and 6 stroke units was explained by SSNAP as an ongoing clinical audit, which gives the opportunity to stroke units to retroactively add in patients they deem were necessary for the audit. The most recent approved data request form can be found in the appendix in chapter 8.

Baseline characteristics recorded by SSNAP on patients are described in table 2.3.2.1

CLINICAL CHARACTERISTIC	VARIABLE TYPE	ADDITIONAL DETAILS
AGE	Categorical	Divided by decades <60 years 61-70 years 71-80 years 81-90 years >90 years
GENDER	Categorical	Male/Female
ETHNICITY	Categorical	Ethnicities included: White Black Asian Mixed Other
CHF	Categorical	Recorded as Yes/No
HYPERTENSION	Categorical	Recorded as Yes/No
ATRIAL FIBRILLATION	Categorical	Recorded as Yes/No
PREVIOUS STROKE	Categorical	Recorded as Yes/No
DIABETES	Categorical	Recorded as Yes/No
NIHSS SCORE	Continuous	Scale from 0 - 42
mRS BEFORE STROKE	Categorical	Ordinal scale from 0 - 5
STROKE SUBTYPE	Categorical	Ischaemic/haemorrhagic
QUARTER OF THE YEAR THE PATIENT WAS ADMITTED	Categorical	Q1 – January to March Q2 – April to June Q3 – July to September

		Q4 – October to December
YEAR OF ADMISSION	Categorical	2013 - 2018
INDEX OF MULTIPLE DEPRIVATION	Categorical	Divided into deciles according to the Ministry of Housing, Communities and Local Government * (129)
DYSPHAGIA	Categorical	Yes/No**
WAS THE PATIENT ALREADY AN INPATIENT	Categorical	Yes/No
STROKE-ASSOCIATED PNEUMONIA	Categorical	Yes/No ***

Table 2.3.2.1 – Description of the baseline characteristics extracted from SSNAP. *Only available in England. ** This derived variable would be defined as the following: dysphagic defined as having had a SALT swallow or were recorded as too medically unwell; not dysphagic defined as SALT swallow assessment not undertake i.e passed bedside swallow test. (SALT defined as Speech and Language Therapist). *** SAP was defined as antibiotic initiation for suspected SAP within the first 7 days from stroke admission

The stroke care processes that were extracted from SSNAP were selected on the basis of the data availability SSNAP offers and on what were most representative of pre-hospital, hyperacute and acute phases of stroke care. The selected care processes can be seen in table 2.3.2.2

CARE PROCESS	VARIABLE TYPE	ADDITIONAL DETAIL
TIME FROM SYMPTOM ONSET OR LAST SEEN WELL TO ARRIVAL AT HOSPITAL	Continuous	Time recorded in minutes
TIME FROM SYMPTOM ONSET OR LAST SEEN WELL TO ARRIVAL AT STROKE UNIT	Continuous	Time recorded in minutes
DID THE PATIENT RECEIVE INTRAVENOUS THROMBOLYSIS	Categorical	Recorded Yes/No
TIME FROM SYMPTON ONSET TO THROMBOLYSIS	Continuous	Time recorded in minutes
TIME FROM ARRIVAL AT HOSPITAL TO STROKE NURSE ASSESSMENT	Continuous	Time recorded in minutes
TIME FROM ARRIVAL AT HOSPITAL TO SWALLOW SCREEN ASSESSMENT	Continuous	Time recorded in minutes
TIME FROM ARRIVAL TO ASSESSMENT BY A PHYSIOTHERAPIST	Continuous	Time recorded in minutes – only available if assessment was performed in the first 72 hours
TIME FROM ARRIVAL TO ASSESSMENT BY A SPEECH AND LANGUAGE THERAPIST	Continuous	Time recorded in minutes – only available if assessment

		was performed in the first 72 hours

Table 2.3.2.2 Description of the stroke care processes extracted from SSNAP.

The clinical outcomes that were extracted from SSNAP are described in table 2.3.2.3

CLINICAL OUTCOME	VARIABLE TYPE	ADDITIONAL NOTES
TIME FROM ADMISSION TO IN-HOSPITAL DEATH	Continuous	Time recorded in minutes
mRS	Categorical	Ordinal scale from 0 - 6
LENGTH OF IN-HOSPITAL STAY	Continuous	Time recorded in minutes

Table 2.3.2.3 Description of clinical outcomes extracted from SSNAP

2.2.3 Data linkage

There was no data linkage to other external datasets such as Hospital Episode Statistics (HES, Office of National Statistics (ONS), or Patient Episode Database for Wales (PEDW) due to governance issues surrounding SSNAP. Other datasets such as HES, ONS and PEDW are not under the purview of HQIP, and thus, authorization was only given by HQIP to access SSNAP data (130-132). There was also no linkage to the organizational audits from SSNAP because the complexity surrounding the data structure, there was no suitable unique identification to link the stroke unit with the trust/hospital. Another reason is that there were three different audits carried in 5 years, and organizational changes occurring at individual hospital and trust level made linkage extremely difficult to impossible to achieve. There were also identification concerns, leaving me with the data structure that I had, which were individual patients nested/clustered within stroke units.

2.2.4 Data Analysis

2.2.4.1 Objective 1 – Description of SAP variation and influence of clinical characteristics on SAP variation

2.2.4.1.1 Aim of the study

The aim of this study was to describe the variation of SAP across stroke units in England and Wales and determine how much of this variation can be attributed to clinical characteristics.

2.2.4.1.2 Study population

As mentioned in section 2.3.2, I included all confirmed strokes recorded in SSNAP from the 1st of April 2013 to the 31st of December 2018. SAP was defined as antibiotic initiation for suspected SAP within the first seven days of admission due to stroke. After initial analysis, a *post-hoc* decision was made to exclude stroke units that saw less than 150 patients per year. This was done to have a more representative sample of stroke units that were dedicated to stroke care, and no units that were repurposed for the occasional stroke patient.

2.2.4.1.3 Outcome

Since this study was looking at SAP variation, the outcome measure defined for this study was SAP, and its definition can be seen in the previous sections.

2.2.4.1.4 Predictor variables

The baseline characteristics selected for this study can be divided into vascular and SAP risk factors. Vascular risk factors included the presence of hypertension, diabetes and congestive heart failure. SAP risk factors included atrial fibrillation, previous stroke or transient ischemic attack (TIA), level of consciousness (LOC = 0 to 3, 3 is completely unconscious), total baseline National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke modified Rankin Scale (mRS), sex, age on admission, and dysphagia. I selected these characteristics due to their known association with the development of SAP and known confounding effects in previous observational studies (41, 59).

2.2.4.1.5 Statistical analysis

Baseline characteristics for both SAP and non-SAP patients were described using simple summary statistics, i.e. frequency tables, mean, median and inter-quartile range. Simple statistics tests, such as t-tests or chi-squared tests were not performed due to the large sample size and complexity of the hierarchical data structure. Any results, including those of small effects sizes, of these tests would likely be significant at the 5% level and biased due to sample size, therefore leading to misleading conclusions.

Due to the binary definition of SAP, a logistic regression model was selected to best fit this outcome. To account for the nesting within stroke units, a multilevel approach was needed to account for this

clustering. Two distinct models were fitted, one with just SAP as an outcome and the stroke unit as the random intercept, and a second one was fitted for the clinical characteristics mentioned beforehand as fixed effect covariates with the stroke unit as the random intercept. OR with 95% CI were reported for each fixed effect covariate. Predicted probabilities for SAP development for each stroke unit were calculated for each model and were compared, ranked and graphed.

Due to the ambiguity regarding the definition of SAP that I had, I decided to perform a sensitivity analysis. Due to the fact that I do not know what day was SAP defined/antibiotics initiated, there was a possibility for misclassification, and the true effect/variation observed could be masked with early death or discharge. The sensitivity analysis excluded patients whose length of stay was under 7 days in order to account for this possibility.

2.2.4.2 Objective 2 – The relationship between stroke care processes and SAP

2.2.4.2.1 Aim of the study

The aim of this study was to investigate the relationship between stroke care processes in the pre-hospital, hyper-acute and acute stroke care phases and the development of SAP. Investigating this relationship was important because the effect modifiable factors have on SAP development is unknown and could play a role in the observed variation studied beforehand.

2.2.4.2.2 Study population

As mentioned in section 2.3.2, I included all confirmed strokes recorded in SSNAP from the 1st of April 2013 to the 31st of December 2018. SAP was defined as antibiotic initiation for suspected SAP within the first seven days of admission due to stroke. After initial analysis, a *post-hoc* decision was made to exclude stroke units that saw less than 150 patients per year. This was done to have a more representative sample of stroke units that were dedicated to stroke care, and no units that were repurposed for the occasional stroke patient. I used the same population as described in section 2.2.4.1.2.

2.2.4.2.3 Outcome variable

The outcome investigated in this study was SAP, as defined beforehand as antibiotic initiation for suspected pneumonia within the first 7 days of stroke admission.

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Due to the pathophysiology of SAP discussed earlier, I decided to focus on 3 distinct phases of stroke care: pre-hospital phase, hyperacute phase and acute phase. Each of the stroke care phases was comprised of distinct key time to event metrics, which were proxies for stroke care processes. For the pre-hospital phase of care, the selected care process was time from symptom onset to arrival at a stroke unit. For the hyper-acute phase of care, the selected care processes were time from arrival at hospital to thrombolysis and time from arrival at hospital to be seen by a nurse or having a a swallow screen (single composite score). For the acute phase of care, the selected care processes were time from arrival at hospital to be seen by a stroke specialist doctor and time from arrival at hospital to be seen by a physiotherapist. Each care process was divided into quartiles to account for outliers in the data. With the exception of time from arrival at hospital to thrombolysis, the first quartile was the reference value. Regarding the thrombolysis covariate, I used not receiving thrombolysis as the reference value, because patients undergoing thrombolysis are subjected to other interventions vs patients that do not undergo thrombolysis. I also included a separate category for unknown times in each stroke care process.

In addition to these stroke care processes, I also used the same SAP and vascular risk factors discussed in section 2.2.4.1.4 to account for potential confounding.

2.2.4.2.5 Statistical analysis

I fitted a multilevel logistic regression model as used in our previous objective, using the previous clinical characteristics as fixed effects covariates and adding these stroke care processes as fixed effects covariates, with the stroke team as the random intercept. Each stroke care processes was added using VanderWeele's principles of confounding in order to avoid adjusting for factors thought to be on the causal pathway (133). Time from symptom onset to arrival at stroke unit was adjusted with only the clinical characteristics mentioned beforehand. Time to thrombolysis was adjusted with time from symptom onset to arrival at stroke unit in addition to the clinical characteristics. Time to

be assessed by a stroke nurse or having a swallow screen (composite) was adjusted with time from symptom onset to arrival at a stroke unit in addition to the clinical characteristics. Time to be assessed by a stroke doctor was adjusted with time to arrival at a stroke unit and time to be assessed by a stroke nurse or having a swallow screen (composite) in addition to the clinical characteristics. Time to be assessed by a physiotherapist was adjusted by all of the aforementioned care processes and clinical characteristics with the exception of time to thrombolysis. OR with 95% CI were reported of each fixed effect covariate.

2.2.4.3 Objective 3 - Impact of SAP on clinical outcomes
2.2.4.3.1 Aim of the study
The aim of this study was to address the implication of SAP on clinical outcomes in stroke patients. Quantifying the extent of the association SAP has on clinical outcomes is important because it could have implications for clinical practice and delivery of stroke unit care.

2.2.4.3.2 Study population
For this study, it is important to mention that there was an amendment done to the dataset that changed the total number of patients and stroke units. This amendment was done because time to in-hospital death was not recorded in the original data request, and an additional request was made to SSNAP which lead to these changes in number. The amended data request can be seen in the appendix Chapter 8.

For this study, I focused on patients with confirmed strokes from the 1st of April 2013 to 31st of December 2018 who were still in hospital between 7 days and 365 days and on stroke units that saw at least 150 patients per year. The stroke unit criteria is the same as described previously in sections 2.2.4.1.2 and 2.2.4.2.2. I focused on these patients because the effect the stroke itself has on the clinical outcomes could mask the effect of SAP on clinical outcomes in the early days of stroke admission. By focusing on patients who were still in hospital after 7 days, the effects of the stroke itself on clinical outcomes have been mitigated, and the effect of SAP on these clinical outcomes is much more visible.

2.2.4.3.3 Outcome variables

For this study, I decided on three important outcomes that have been used in previous studies, clinicians have used previously and were available in SSNAP. These were length of in-hospital stay, mRs on discharge and in-hospital mortality. As mentioned previously, length of in-hospital stay and in-hospital mortality were extracted in minutes by SSNAP, but were converted into days for analysis. MRs on discharge was measured on an ordinal scale, from 0-6.

2.2.4.3.4 Predictor variables

For this study I used the same vascular and SAP risk factors mention in sections 2.2.4.1 and 2.2.4.2. In addition to these risk factors, I included markers of care derived from SSNAP's markers of good quality stroke care. These were arrival at a stroke unit within 4 hours from symptom onset (Yes/No), received a swallow screen within 4 hours from admission (Yes/No) , assessment by a physiotherapist, speech and language therapist and an occupational therapist within 72 hours from admission (all in a single composite binary score – Yes – was seen by all therapists in 72 hours, No – was not seen by all therapists in 72 hours) and if the patient received thrombolysis (Yes – patient received thrombolysis, No – the patient did not receive thrombolysis).

2.2.4.3.5 Statistical analysis
2.2.4.3.5.1 Length of in hospital stay

Length of stay in hospital measured in days was a count variable, as such, a negative binomial model was selected to analyse this outcome. I selected a negative binomial model instead of a Poisson model because a negative binomial model allows for more flexibility of the data compared to a Poisson model. To account for the clustering, a multilevel approach was also selected for this outcome. To explore the full extent of the association between SAP and length of stay in hospital, I modelled the data in three distinct phases. Firstly as an only intercept model, being stroke unit as the random intercept. A second model using the vascular and SAP risk factors mentioned in 2.2.4.3.4 as fixed effect covariates with the stroke unit as the random intercept. The final model included vascular and SAP risk factors and stroke care markers mentioned in 2.2.4.3.4 included as fixed

effects covariates in this model. Incidence rate ratios (IRR) with 95% CI were reported for this clinical outcome.

2.2.4.3.5.2 mRs on discharge

MRs on discharge is measured as an ordinal scale, ranging from 0 – 6 where 0 is no functional disability, and 6 is death. An ordinal regression model was selected to best fit this outcome. To account for the clustering in stroke units, a multilevel approach was also used. To explore the full extent of the association between SAP and mRs on discharge, I modelled the data in three distinct phases. Firstly as an only intercept model, being stroke unit as the random intercept. A second model using the vascular and SAP risk factors mentioned in 2.2.4.3.4 as fixed effect covariates with the stroke unit as the random intercept. The final model included vascular and SAP risk factors and stroke care markers mentioned in 2.2.4.3.4 included as fixed effects covariates in this model. OR with 95% confidence intervals were reported for each fixed effect.

2.2.4.3.5.3 In-hospital mortality

In-hospital mortality was measured as time to in-hospital death in days. A multilevel parametric survival analysis model was selected to best fit this data. A parametric survival analysis model was selected instead of a Cox hazard model because I believed the parametric survival analysis model better represented the data because I did not believe the proportional hazard function would hold over the 365 day follow up. To explore the full extent of the association between SAP and in-hospital mortality, I modelled the data in three distinct phases. Firstly I modelled SAP by itself with the stroke unit as the random intercept. A second model using the vascular and SAP risk factors mentioned in 2.2.4.3.4 as well as SAP as fixed effect covariates with the stroke unit as the random intercept. The final model included SAP, vascular and SAP risk factors and stroke care markers mentioned in 2.2.4.3.4 included as fixed effects covariates in this model. HR and 95% CI were reported for each fixed effect. A Kaplan-Meier curve comparing the survival estimates between SAP and non-SAP patients was also reported.

2.2.5 Missing data

There were various levels of data completeness across the dataset, and this caused several issues for the data analysis. Several steps were taken into account to address each issue in each objective. In objective 1, total NIHSS score was the variable that had the most missing data, with over 100,000 patients missing their NIHSS score. I excluded these patients from our analysis in objective 1 because I wanted to have a continuous variable that was more representative of stroke severity when discussing SAP variation. For objective 2, I created a categorical version of NIHSS score to address this issue, because compared to study 1, there were more variables with missing data, so I tried to "save" as much of my sample as possible to have a more accurate representation of the effect of the care process on SAP development. NIHSS was divided according to stroke severity (134), with mild stroke being classified with an NIHSS between 0-4, a mild to moderate stroke being classified with an NIHSS between 5 -15, a moderate to severe stroke being classified with an NIHSS between 16 – 20, and a severe stroke being classified with an NIHSS >21. An added category of missing NIHSS value was also added to this categorization. In objective 2, as mentioned beforehand, several care processes had missing data for various reasons, such as unknown times to event or if the patient did not receive the care process. I addressed this when I performed the categorization of the stroke care processes. As mentioned beforehand, the categorization into quartiles of each stroke care process also led to the development of a separate category including these missing or unknown times. This was to allow an interpretable incorporation of the unknown or unrecorded cases into my analysis.

2.2.6 Ethics and dissemination

Data access was granted via an HQIP data request. Ethics approval for this section of the project was not deemed necessary.

2.3 Survey methods

2.3.1 Main aim

The main aim of the survey was to explore the different characteristics (including thresholds when applicable) used by clinicians when considering antibiotic initiation for SAP.

2.3.2 Study design

A cross-sectional survey of UK clinicians working in stroke care was performed to assess their approach to diagnosis and antibiotic initiation for suspected SAP. The survey consisted of four case scenarios of varying SAP ambiguity, based on the PISCES criteria for diagnosis (9). Scenario 1 contained a patient with features of definite SAP, whereas the following three scenarios changed patient characteristics, stroke characteristics, symptoms, signs and investigation results so that probable or definite PISCES criteria were not met. In each scenario, if antibiotics were not initiated, respondents were offered additional options which further modified symptoms, signs, or investigations (including thresholds where applicable) and asked if they wanted to reconsider their initial decision regarding antibiotic initiation.

A full description of the characteristics and division of the scenarios is presented in Chapter 5.

Scenario	Description
1	A 73-year-old admitted to the HASU for TACI 4 days ago, with an NIHSS of 16, presents with a temperature of 38.5°, a RR of 26/ minute, unilateral crackles and purulent cough. Investigations included a chest X-ray showing infiltrates in the inferior right lobe, PaO2 measured at 85 mmHg on room air and CRP of 75 mg/L.
2	A 55-year-old patient, who was admitted into the HASU for a LACI 4 days ago with an NIHSS of 11, presents with coughing, a temperature of 38 degrees Celsius and a respiratory rate of 20/minute. The junior doctor on call decided to organize further investigations, which included a chest x-ray with no abnormalities and a CRP measured at 25 mg/L.
3	A 93-year-old patient admitted to the HASU with a POCI 4 days ago and an NIHSS of 5, presents with a temperature of 36.5 degrees Celsius, cough, unilateral crackles and a respiratory rate of 17/ minute. The junior doctor on-call sent a chest x-ray and it showed no abnormalities. Additional tests include a total WBC of 10.7×10^9/L.
4	An 85-year-old patient who was admitted to the HASU due to a TACI 4 days ago with an NIHSS of 21, presents with a temperature of 37 degrees Celsius, a respiratory rate of 20/minute, O2 saturation level of 92% on room air, and dysphagia after a SLT assessment. No other respiratory symptoms are present. The junior doctor on call decided to send a chest x-ray and it shows no abnormalities. Additional tests include a CRP measured at 75 mg/L.

Table 2.3.2.1. Description for each of the scenarios in our study. HASU – Hyperacute stroke unit,

TACI – total anterior circulation infarct, NIHSS – National institute of health stroke scale, PaO2 –

Oxygen arterial pressure, CRP – C-reactive protein, LACI – lacunar infarct, POCI – posterior circulation

infarct, WBC – white blood cell count, SLT- Speech and Language Therapist

Information asked of survey participants included profession, hospital location (135) and years of

experience since qualifying (136). The study was considered by the ethics committee of the Division

of Cardiovascular Sciences at the University of Manchester, but no ethical approval was required. The survey was developed using Select Survey software and piloted twice with three consultant stroke physicians at Manchester Centre for Clinical Neurosciences, Salford Royal Hospital. Changes to the phrasing of the question and the scenarios were adopted accordingly after each round of piloting.

2.3.3 Data collection

The survey was distributed via social media, and directly to members of the British Association of Stroke Physicians (BASP) and NHS Getting It Right the First Time (GIRFT) network. Some overlap in membership was present between BASP and GRIFT due to their respective audiences. Both organizations distributed the survey via email twice, on the 1st of December 2019 and the 4th of January 2020. The survey was open to responses from 1st of December 2019 to 1st of February 2020. The survey was closed early due to lockdown measures and increased influence of the SARS-Cov-2 pandemic, resulting in changes from research duties to active clinical duties to our participants.

2.3.4 Data analysis

Descriptive statistics were calculated for the participant characteristics and clinical scenario responses. The level of agreement compared to random chance alone among participants for antibiotic initiation as the patient was described in each scenario was calculated using a multi-rater Kappa statistic. This was calculated overall and split for rater characteristics as consultants and non-consultants.

2.4 Implications for selected methodology

2.4.1 Implications for data analysis regarding SSNAP

Selecting SSNAP as data provider had several implications on my study. SSNAP focuses heavily on data from England and Wales, and until 2017, it started including data from stroke centres in

Northern Ireland. The most important implication is that I would be using data from one of the largest stroke register in the UK, but would be excluding data from Scotland, and therefore it would not be reflective of stroke care of the UK as a whole. Secondly, SSNAP was designed for another purpose in mind: quality improvement based on the ICSWP key criteria. While it is an optimal source of information for this purpose, when attempting to answer other research questions using this dataset that was not designed with this in mind, leads to limited answers.

Another important implication that needs addressing is the categorization of missing data instead of imputation or complete case analysis. It is important to note that during the analysis, it was noted that several variables had missing data to varying degrees of completeness. Being such a large dataset and wanting to have a more accurate rendition of what happens in a real world setting, I decided to exclude the method of imputation or complete case analysis. Using a complete case analysis would have excluded approximately 300,000 datapoints from my analysis, rendering my conclusions extremely limiting. Using imputation would have used the assumption that the data that was missing was not missing at random, which was not an assumption I could make in my dataset. Therefore, I decided to categorize my missing data and have it as an interpretable characteristic of my data analysis as was described previously.

Another important implication that needs to be addressed is the exclusion of smaller stroke units from the data analysis. This decision would have important consequences in the data analysis and interpretation of the results. By excluding these smaller stroke units, there is a possibility of missing data that can be reflective of other care practices in these smaller units. However, these smaller units would not be representative of the practices of stroke care in England and Wales. Future research into how these smaller units fare compared to the larger units and if specific care practices need to be adjusted for these smaller units is a possibility that needs to be explored in the future.

In addition to this exclusion, it is important to mention the approach described in section 2.2.4.3. By excluding patients whose length of stay was less than 7 days, there was the assumption that the

effect caused by the stroke severity associated with clinical outcomes would be mitigated. This way the effect seen in my analysis would be more reflective of SAP on clinical outcomes. However, excluding these patients would also exclude patients that could have developed SAP and have died within the first 7 days. Pathophysiologically, SAP usually develops within the first 72 hours, so there is a possibility of the effect of SAP could be seen within the first 7 days. This limitation is plausible and needs to be mentioned beforehand.

2.4.2 Implications of survey approach

To address the question of clinician behaviour, there were 2 potential avenues of research: the survey approach or a focus group approach. The focus group approach could've added more detail to the different characteristics and thresholds used for antibiotic initiation, however, there was little evidence suggesting that using this approach would be representative of the whole clinician population of the UK. This is what led to the survey approach; approaching a larger population that was based all over the UK could provide a more representative view of clinician behaviour compared to a focus group. However, this approach has its drawbacks, specifically an increased number of non-responders, difficulty in engaging the target audience and non-completers. However, I still decided to go with this approach because I wanted to engage as many clinicians as possible to have as a broader view as possible to complement the findings of the SSNAP dataset analysis.

2.5 Statistical software

All statistical analysis from this thesis was performed in Stata IC v.14.

Chapter 3 - Variation of stroke associated pneumonia across stroke units in England and Wales: A registry based cohort study

3.1 Preface

This chapter is going to focus on answering the question of SAP variation across England and Wales and to what extent do clinical characteristics modify the observed variation. This chapter is paramount, as it is the basis for the rest of this thesis moving forward.

3.2 Abstract

3.2.1 Background

Pneumonia is common in stroke patients and is associated with worse clinical outcomes. Prevalence of stroke associated pneumonia (SAP) varies between studies, and reasons for this variation remain unclear. We aimed to describe the variation of observed SAP in England and Wales and explore the influence of patient baseline characteristics on this variation.

3.2.2 Methods

Patient data was obtained from the Sentinel Stroke National Audit Programme for all confirmed strokes between 1 April 2013 to 31 December 2018. SAP was defined by new antibiotic initiation for pneumonia within the first 7 days of admission. The probability of SAP occurrence within stroke units was estimated and compared using a multilevel mixed model with and without adjustment for patient level characteristics at admission.

3.2.3 Results

Of the 413,133 patients included, median NIHSS was 4 (IQR 2-10) and 42.3% were aged over 80 years. SAP was identified in 8.5% of patients. The median within stroke unit SAP prevalence was 8.5% (IQR 6.1% - 11.5%) with a maximum of 21.4%. The mean and variance of the predicted SAP probability across stroke units decreased from 0.08 (0.68) to 0.05 (0.63) when adjusting for patient admission characteristics. This difference in the variance suggests that clinical characteristics account for 5% of the observed variation in SAP between units.

3.2.4 Conclusions

Patient level clinical characteristics contributed minimally to the observed variation of SAP between stroke units. Additional explanations for the observed variation in SAP need to be explored which could reduce variation in antibiotic use for stroke patients.

3.3 Introduction

In this chapter I address objective 1 mentioned in chapters 2 and 3. As mentioned previously, SAP occurs in around 14% of patients (76) although there is marked variation in reported frequency between observational studies, registries and within registries, where SAP frequency in observational studies ranged from 5.3% to 37.9% and in registries from 6.7% to 30% (35, 36). The underlying reasons for this variation are uncertain, but could include potentially modifiable or non-modifiable factors. Baseline characteristics, such as increased stroke severity, increased age and dysphagia (36) are consistently associated with SAP and might therefore contribute to variation in reported SAP frequency. Seasonality may also contribute to this variation (137). However, other factors contributing to variation in observed SAP between studies or units could be modifiable differences in care processes (e.g. monitoring of vitals or swallow screening protocols), approaches to diagnosis and thresholds for initiating antibiotics (physician diagnosis v. application of standardised algorithms) (123, 138).

Better understanding the underlying variation in SAP is important if modifiable factors can be identified. This could lead to avoidance of over or under-treatment of SAP, improved antibiotic stewardship, reduced antibiotic resistance, and improved clinical outcomes. A key first step is determining how much variation is accounted for by non-modifiable clinical characteristics. The aim of this study is to therefore describe the variation of SAP between stroke units and determine how much this variation can be explained by patient baseline clinical characteristics. Our objectives were to first describe the observed variation of SAP across stroke units in England and Wales participating in a large national registry; and then to compare the estimated probabilities of developing SAP across stroke units adjusted and unadjusted for patient level characteristics.

3.4 Methods

3.4.1 Study design and data source

I undertook an observational cohort analysis, using anonymized, patient-level and unit-level data from the Sentinel Stroke National Audit Programme (SSNAP) database. SSNAP is a national audit of stroke care created in 2013 in association with the Intercollegiate Stroke Working Party. Data transfer from SSNAP for the study was approved by the Healthcare Quality Improvement Partnership (HQIP). Data access requests should be directed to HQIP as the joint data controller and SSNAP as the data provider. All stroke units in England, Wales and Northern Ireland are required to provide patient characteristics, processes of care, and specified outcome measures. We requested initial admission patient level SSNAP recorded and derived variables. Patients were included if presenting with ischaemic or haemorrhagic stroke to a stroke unit between 1 April 2013 to 31 December 2018 in England and Wales. Stroke units with less than 150 patients per year in the five-year period were excluded *post-hoc* in order to better reflect established specialist stroke units. Observed SAP was defined as those patients recorded as having new antibiotic initiation for pneumonia within the first seven days of stroke admission. Dysphagia was defined in patients with a baseline swallow screen followed either by a speech and language therapist (SLT) assessment or no SLT assessment due to being 'too unwell' or for organisational reasons (43).

3.4.2 Statistical analysis

Descriptive statistics were used for baseline clinical characteristics, including the distribution of observed SAP cases per year across stroke units. Stroke patients are clustered within stroke units. To account for this lack of independence between stroke patients whilst accounting for confounding, a multilevel mixed effects logistic regression model was fitted. The random effects intercept present in the model accounts for the within and between variation present within the stroke unit clusters. Two models were fitted, one without (unadjusted) and one with (adjusted) fixed effect covariates. Through modelling only the stroke units as a random effects intercept, we estimated the predicted probability of SAP across stroke units without adjusting for clinical factors. To investigate the

influence of stroke patient characteristics, the fixed effects covariates were identified *a priori* to include vascular and SAP risk factors at baseline entry. Vascular risk factors included the presence of hypertension, diabetes and congestive heart failure. SAP risk factors included atrial fibrillation, previous stroke or transient ischemic attack (TIA), level of consciousness (LOC = 0 to 3, 3 is completely unconscious), total baseline National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke modified Rankin Scale (mRS), sex, age on admission, and dysphagia.

Odds ratios (ORs) with 95% confidence intervals (CIs), intra-class correlation coefficient (ICC), and cluster variance were reported and compared for the two models where appropriate. Predicted probabilities from the unadjusted and adjusted model were calculated and ranked (smallest to largest) and plotted for the stroke units. Patients discharged from hospital care before 7 days may subsequently develop SAP and thus be misclassified. We therefore performed an additional sensitivity analysis where patients' length of stay was greater than or equal to 7 days post first admission. Statistical analysis was performed using Stata IC version 14.

3.5 Results:

456,590 stroke patients across 322 units were identified, of which 39397 (8.73%) had observed SAP after 5200 patients were excluded due to missing SAP identification data. A further 153 stroke units (38257 patients) with ≤ 150 patients per year were excluded, leaving 413,133 patients of which 34987 (8.47%) had observed SAP. A full description of baseline characteristics are presented in Table 3.4.1. Of the female patients, 17980 (8.76%) developed SAP, while 17007 (8.00%) of the male patients developed SAP, of those patients over 80 years of age, 21359 (13.9%) developed SAP, 31889 (8.53%) of patients of white ethnicity developed SAP, 29460 (8.04%) of patients admitted due to ischaemic stroke developed SAP. The median admission NIHSS of patients who developed SAP was 14 (Interquartile range, IQR 6-20).

The total number of observed SAP episodes across 169 stroke units ranged from 4 to 860 for the 5-year period. A histogram of the number of observed SAP episodes for each stroke unit is plotted in

Figure 3.4.1. The median number of observed stroke unit SAP episodes per year was 29.8 (IQR 20.8-44.5). The observed SAP prevalence per year ranged from 0.82% to 21.4%, with the median prevalence 8.50% (IQR 6.06% - 11.5%).

Both regression models were applied to the same complete cases population group of 341740 patients across 169 units after accounting for missing data. Table 3.4.2 reports OR and 95% CIs from the adjusted mixed logistic regression model. Several factors were associated with SAP, including atrial fibrillation (OR 1.2, 95% CI 1.1-1.2), congestive heart failure (OR 1.3, 95% CI 1.2-1.4), dysphagia (OR 3.8, 95% CI 3.7-3.9) and NIHSS score on arrival (OR 1.06, 95%CI 1.06-1.07). The estimated predicted probability of SAP per stroke unit in the unadjusted model ranged from 0.004 to 0.25, compared to 0.001 to 0.21 in the adjusted model. The (unadjusted) median SAP probability was 0.07 (IQR 0.05 – 0.11) whereas the adjusted was 0.04 (IQR 0.03 – 0.07). The mean and variance of the predicted SAP probability across stroke units decreased from 0.08 (0.68) to 0.05 (0.63) when adjusting for patient admission characteristics. Unadjusted variance was 0.68 (95% CI 0.53-0.89) and adjusted variance was 0.63 (95% CI 0.549 – 0.81). This change in variance indicates that clinical characteristics account for 5% of observed variation. Figure 3.4.2 (A) and (B) plot the predicted probabilities (and 95% CIs) across modelled stroke units for both models. Figure 3.4.3 presents the spread of the data for both the unadjusted and adjusted probabilities. Intraclass correlation value for the unadjusted model was 0.17 (95% CI 0.14 – 0.21), while the intraclass correlation value for the adjusted model was 0.16 (95% CI 0.13 – 0.20).

The number of patients who left hospital prior to 7 days was 186633 (45.2 %), leaving the sensitivity analysis with 33076 (14.3%) patients with SAP and 195074 (84.4%) non-SAP patients. Results from the sensitivity analysis were comparable to our main findings, indicating misclassification of SAP patients was minimal.

	non-SAP	SAP	Missing
Total number	378146 (91.5%)	34987 (8.47%)	4777 (1.14%)
Female	184734 (90.0%)	17980 (8.76%)	2524 (1.22%)
Male	193412 (90.9%)	17007 (8.00%)	2253 (1.05%)
Age on arrival			
<60	58604 (95.9%)	1846 (3.02%)	687 (1.12%)
60-69	63839 (93.9%)	3395 (4.99%)	741 (1.09%)
70-79	102229 (91.4%)	8397 (7.51%)	1182 (1.05%)
80-89	114011 (87.5%)	14646 (11.2%)	1571 (1.20%)
>90	39463 (84.3%)	6713 (14.3%)	596 (1.27%)
Ethnicity			
White	337526 (90.4%)	31889 (8.53%)	4118 (1.10%)
Asian	10919 (92.1%)	756 (6.38%)	177 (1.49%)
Black	4617 (93.7%)	252 (5.11%)	60 (1.21%)
Mixed	1272 (90.5%)	110 (7.82%)	24 (1.71%)
Other	23812 (90.9%)	1980 (7.56%)	398 (1.52%)
CHF	19022 (85.2%)	2986 (13.4%)	306 (1.37%)
Hypertension	202701 (90.3%)	19232 (8.57%)	2432 (1.08%)
Diabetes	78158 (90.4%)	7390 (8.54%)	933 (1.07%)
Atrial Fibrillation	71285 (86.0%)	10501 (12.7%)	1056 (1.27%)
Previous stroke or TIA	99885(89.9%)	10029 (9.03%)	1196 (1.08%)
Stroke subtype			
Infarction	333119 (90.9%)	29460 (8.04%)	3863 (1.05%)
Primary ICH	42272 (87.3%)	5321(11.0%)	814 (1.68%)
mRS before stroke			
0	212719 (93.1%)	13156 (5.76%)	2524 (1.11%)
1	57772 (90.4%)	5439 (8.51%)	680 (1.06%)
2	38017 (87.9%)	4765 (11.0%)	485 (1.12%)
3	41547 (85.4%)	6531 (13.4%)	581 (1.20%)
4	21678 (83.6%)	3898 (15.0%)	360 (1.39%)
5	6413 (82.7%)	1198 (15.4%)	147 (1.89%)
NIHSS on arrival (median, IQR)	4 (2 -9) n=330710	14 (6 - 20) n= 27800	-
Level of Consciousness			
0	326642 (93.0%)	21050 (6.00%)	3370 (0.96%)
1	29579 (77.0%)	8223 (21.4%)	609 (1.59%)
2	12384 (74.0%)	4025 (24.0%)	328 (2.00%)
3	9541 (81.5%)	1689 (14.4%)	470 (4.02%)
Dysphagic	14394 (32.4%)	27405 (61.7%)	2614 (5.89%)

Table 3.5.1. Baseline characteristics of SAP patients. CHF – Congestive Heart Failure, TIA – Transient Ischaemic Attack, ICH – Intracerebral haemorrhage, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale, IQR – Interquartile range
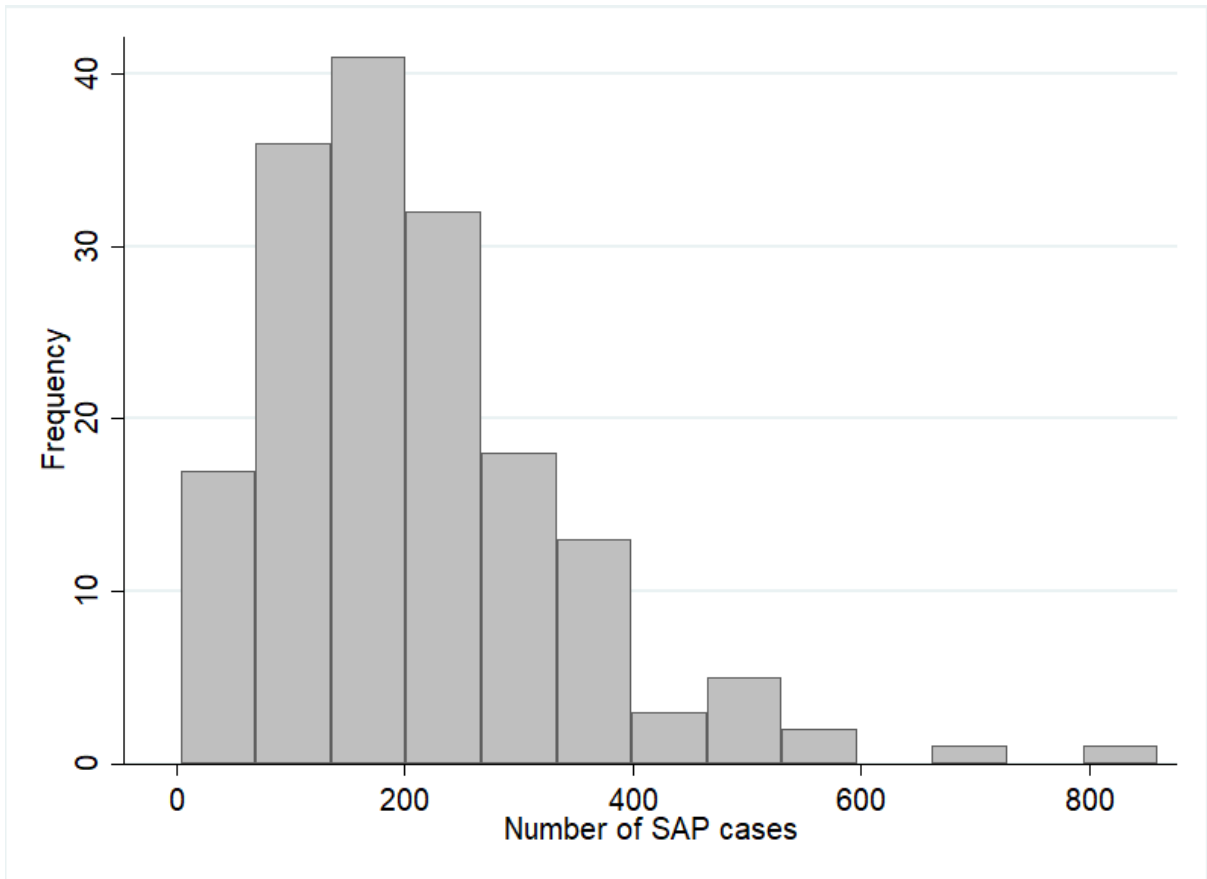
Figure 3.5.1. Histogram showing the distribution of the average number of observed SAP episodes per year for each stroke unit

Predictors	Odds Ratio	95% Confidence Interval	Unadjusted model	95% Confidence Interval
Age on arrival				
<60	1.00 (reference)	-	-	-
60-69	1.5	(1.4 to 1.6)	-	-
70-79	2.0	(1.9 to 2.1)	-	-
80-89	2.5	(2.3 to 2.6)	-	-
>90	2.5	(2.3 to 2.6)	-	-
Modified Rankin Scale Score on Arrival				
0	1.00 (reference)	-	-	-
1	1.3	(1.2 to 1.3)	-	-
2	1.4	(1.3 to 1.5)	-	-
3	1.4	(1.4 to 1.5)	-	-
4	1.3	(1.2 to 1.3)	-	-
5	1.1	(0.96 to 1.1)	-	-
Female sex	0.72	(0.71 to 0.75)	-	-
Atrial Fibrillation	1.2	(1.1 to 1.2)	-	-
Previous Stroke or TIA	0.92	(0.89 to 0.94)	-	-
Congestive Heart Failure	1.3	(1.2 to 1.4)	-	-
Hypertension	0.99	(0.96 to 1.0)	-	-
Diabetes	1.1	(1.0 to 1.1)	-	-
Level of consciousness				
0	1.00 (reference)	-	-	-
1	1.4	(1.4 to 1.5)	-	-
2	1.1	(1.0 to 1.1)	-	-
3	0.35	(0.32 to 0.38)	-	-
Dysphagia	3.9	(3.8 to 4.0)	-	-
NIHSS score	1.06	(1.05 to 1.07)	-	-
Variance	0.63	(0.49 to 0.81)	0.68	(0.52 to 0.89)
Random intercept coefficient	-4.4	(-4.5 to -4.3)	-2.2	(-2.3 to -2.2)
Intra-class correlation coefficient	0.16	(0.13 to 0.20)	0.17	(0.14 to 0.21)

Table 3.5.2. Multivariable multilevel logistic regression Odds ratios for the predictor variables for SAP. TIA – Transient Ischaemic Attack, NIHSS – National Institute of Health Stroke Scale

A)
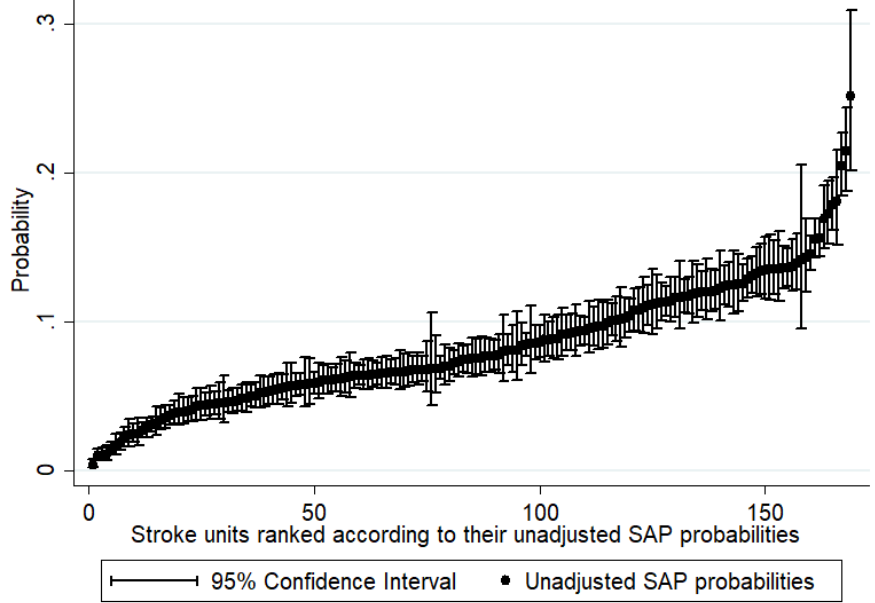
B)
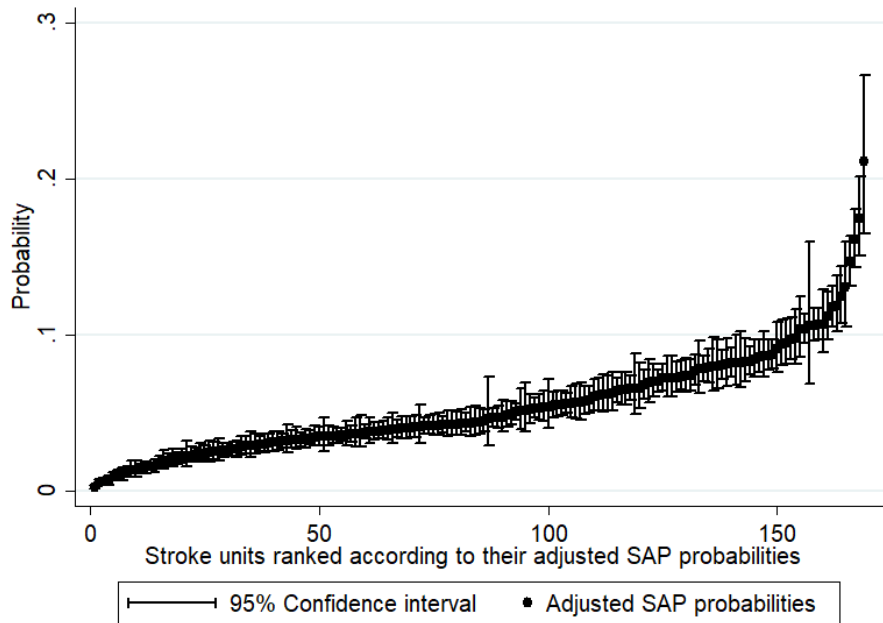
Figure 3.5.2. Stroke units ranked according to their (A) unadjusted SAP probabilities and (B) adjusted SAP probabilities with their corresponding 95% confidence intervals
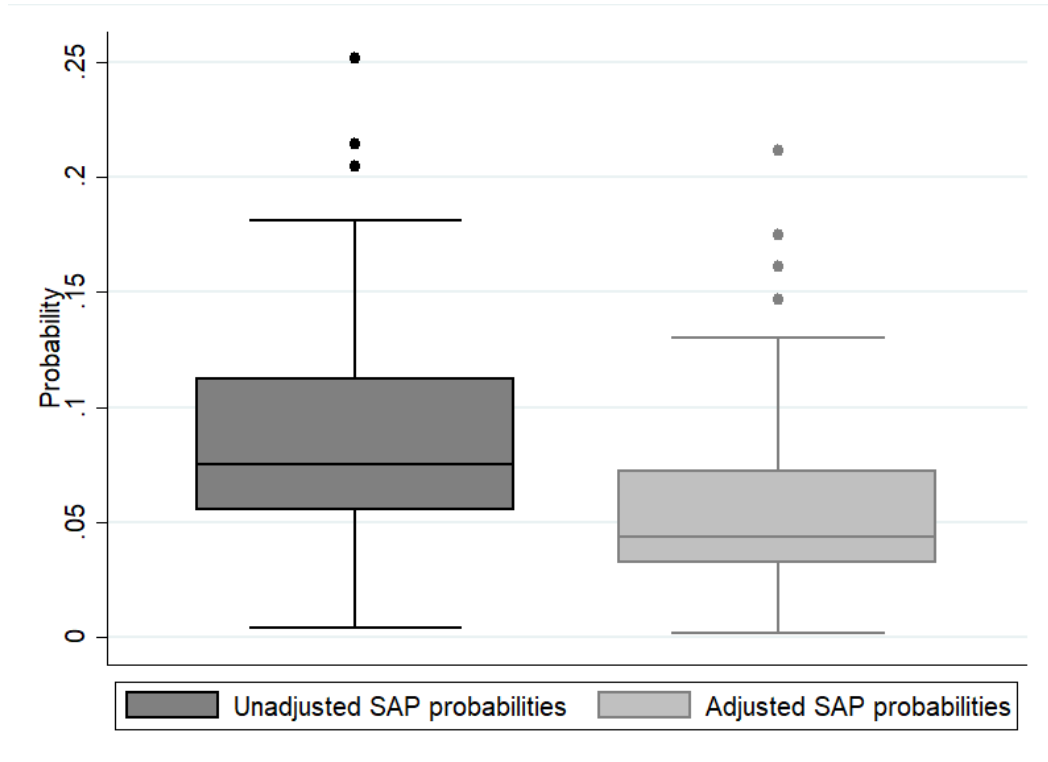
Figure 3.5.3. Box plots comparing unadjusted SAP probabilities vs adjusted SAP probabilities

Predictors	Odds ratio	95 % Confidence Interval
Age on arrival		
<60	1.0 (reference)	-
60-69	1.5	(1.4 to 1.6)
70-79	1.8	(1.7 to 1.9)
80-89	2.0	(1.9 to 2.2)
>90	2.1	(1.9 to 2.2)
Modified Rankin Scale Score on Arrival		
0	1.0 (reference)	-
1	1.2	(1.1 to 1.2)
2	1.2	(1.2 to 1.3)
3	1.2	(1.2 to 1.3)
4	1.2	(1.1 to 1.2)
5	1.1	(1.0 to 1.2)
Female	0.71	(0.69 to 0.73)
Atrial Fibrillation	1.1	(1.1 to 1.2)
Previous Stroke or TIA	0.91	(0.88 to 0.94)
Congestive Heart Failure	1.3	(1.2 to 1.3)
Hypertension	0.99	(0.96 to 1.0)
Diabetes	1.0	(0.98 to 1.1)
Level of consciousness	0.91	(0.89 to 0.93)
Dysphagia	3.1	(3.0 to 3.2)
NIHSS score	1.03	(1.03 to 1.04)
Variance	0.62	(0.49 to 0.79)

Table 3.5.3. Sensitivity analysis regression results

3.6 Discussion

Our findings show that there is substantial variation of observed SAP episodes, and therefore antibiotic use for pneumonia, across stroke units in England and Wales. This could be of major importance if it reflects under- or over-treatment with antibiotics. We also found that predicted probabilities of SAP were minimally modified after adjustment for patient level clinical characteristics. This implies that differences in patient characteristics that are associated with risk of SAP contributed only marginally to the between unit variation in SAP. This is important because it suggests that additional, potentially modifiable factors account for most of the variation.

Several other factors could be important contributors to the observed variation in SAP. First, there is known variation in how clinicians diagnose SAP, with approaches ranging from non-standardised diagnosis (physician diagnosis) to application of various algorithm-based criteria such as the Centres for Diseases Control and Prevention (CDC) criteria or the American Thoracic Society and Infection Diseases Society of America (ATSIDS) criteria (35). This is of relevance as clinicians tend to overdiagnose SAP when compared to application of an established algorithm (123). There is also evidence that the thresholds for diagnosing SAP and initiating antibiotics is linked to clinician behaviours, with weighting towards particular variables such as stroke severity and C-reactive protein concentration (138). Perceived futility in patients with severe stroke and multiple comorbidities could lead to clinicians withholding antibiotics. Secondly, seasonality could also influence this variation. The microbiological aetiology of SAP incorporates organisms associated both with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (86). CAP is frequently viral, and viral contributions to SAP linked to seasonal occurrence of CAP or viral lower respiratory tract infections has not been investigated. A third potential explanation could be differences in stroke unit care and processes between stroke units. Several components of stroke care, and how quickly, consistently or effectively they are delivered may influence development of SAP. For example, delays in dysphagia assessment have been associated with increased risk of SAP (72). High-volume thrombolysis and thrombectomy units with good outcomes are likely to be

associated with lower incidence of SAP (139, 140). Further evaluation is needed on the impact of multi-disciplinary team interventions such as positioning, nasogastric tube feeding or early mobilisation on SAP development (102), as well as the impact of organizational level factors such as staffing levels.

Several patient level characteristics included in this study were associated with increased odds of SAP, among them NIHSS score and level of consciousness, increased age, higher preceding modified mRS score, congestive heart failure, diabetes, atrial fibrillation and dysphagia. These characteristics have already been described in previous studies and generally found to be associated with increased risk of SAP (38, 40, 42). Our findings are consistent with previous research, which highlight the importance of these clinical predictors. However, an unexpected finding was that previous stroke or TIA was not associated with SAP. This contrasts with previous evidence (65), and the reasons for this in our study are not clear and should be interpreted with caution. One possible issue is the heterogeneity of the variable, as previous TIA or stroke may affect the risk of developing SAP differently but was not differentiated. Important factors such as the subtype, occurrence of >1 previous stroke, residual neurological deficit and when the previous event occurred were not recorded. Another possible explanation for our findings is the table 2 fallacy (141). This is where the effects estimates that we are reporting are those of our SAP outcome variable and do not represent the effect of previous stroke or TIA that has also undergone stroke severity adjustment. This table 2 fallacy, where there is interpretation of direct effects as total effects. Such effect estimates represent the direct effect between the covariate and outcome and is not representative of the total effect of the confounder, which may include the 'indirect' effect between confounder and outcome via the main predictor. In our specific case with previous stroke, the 'total' effect of this covariate may be comprised of the 'direct' effect with SAP outcome and the 'indirect' effect via stroke severity at baseline, as previous stroke is likely to be correlated with both.

The clinical impact and implications of our findings require consideration. SAP is consistently associated with adverse clinical outcomes, including increased mortality, healthcare costs and worse functional outcome in survivors (76, 115). Antibiotic usage, and in particular concerns around antibiotic over-use and antimicrobial resistance, are major global public health concerns (112). However, under-treatment of SAP may also impact clinical outcomes. How our observed variation in SAP episodes relates to clinical outcomes is unclear and requires further study. Strategies to reduce over-diagnosis or treatment of SAP, whilst not compromising clinical outcomes, could have significant impact on antibiotic stewardship, reducing antibiotic and healthcare costs and antimicrobial resistance. Identification of other stroke unit practices or interventions associated with variation in SAP could stimulate quality improvement initiatives or trials.

Our study contains several strengths, including a large sample size over several years and a large proportion of the target stroke population, with high case ascertainment, improving the generalisability of our findings. SSNAP also records a number of patient characteristics that are reproducible clinical predictors of SAP (38, 40). However, our study also has several limitations. Firstly there is no record of diagnostic approach or decision-making processes used by clinicians to initiate antibiotic treatment and therefore observed SAP episodes. Second, methods for capturing SAP episodes for SSNAP entry may differ between units, which could lead to under-reporting relating to consistency of coding. As SAP episodes in SSNAP are based on new antibiotic initiation, withholding antibiotics due to perceived futility in patients with severe stroke and a clinical diagnosis of SAP would also lead to underestimates of SAP frequency. There are also limitations within the completeness of the dataset in several measured variables with the most notable being the NIHSS score. Another is the reliability of some of the included variables, particularly derived dysphagia status. As dysphagia is not recorded directly in SSNAP, derivation of dysphagia could have misclassified some patients. The patient level clinical characteristics in our models were limited by the variables recorded in SSNAP, or derived from them. Several variables that have been associated with SAP are not recorded in SSNAP, most notably chronic obstructive pulmonary disease (COPD)

and smoking status. These two characteristics have previously been associated with increased risk of developing SAP (42), and could have contributed to the variation in SAP between stroke units. Other variables such as oncological status, immunological status and vascular risk factors which have been associated with pneumonia are not recorded in SSNAP (56, 59), and could limit our conclusions.

3.7 Conclusions

Large variation of SAP, and therefore antibiotic use, has been observed between stroke units during a five-year period in England and Wales. This variation can be accounted for, to a limited extent, by patient level clinical characteristics alone. However, further research is needed to determine additional factors contributing to this variation, such as diagnostic approach, clinician behaviours, organisational aspects of stroke care, patient care processes, seasonal factors and potentially modifiable factors that could have an impact on SAP variation.

Chapter 4 – The timing of stroke care processes and development of stroke associated pneumonia: a national registry cohort study

4.1 Preface

In the previous chapter, I determined that there is widespread variation of SAP across England and Wales and non-modifiable characteristics, i.e, clinical characteristics accounted minimally for the observed variation. It therefore opens the question what other factors could be involved in this variation and what other factors could be associated with the development of SAP that could be driving this variation. In this chapter, I attempt to answer this question by looking at the stroke care perspective, to determine whether stroke care processes have a role to play in the development of SAP.

4.2 Abstract

4.2.1 Introduction

Timely stroke care can result in significant improvements in stroke recovery. However, little is known about how stroke care processes relate to complications such as the development of stroke associated pneumonia (SAP). Here we investigated associations between stroke care processes, their timing and development of SAP

4.2.2 Methods

We obtained patient-level data from the Sentinel Stroke National Audit Programme for all confirmed strokes between 1st April 2013 and 31st December 2018. SAP was identified if new antibiotic initiation for pneumonia occurred within the first 7 days of admission. Time to key stroke care processes in the pre-hospital, hyperacute and acute phase were investigated. A mixed effects logistic regression model estimated the association between SAP (Odds ratios [OR] with 95% CI) and each process of care after controlling for pre-determined confounders such as age, stroke severity and comorbidities.

4.2.3 Results

SAP was identified in 8.5% of 413,133 patients in 169 stroke units. A long time to arrival at a stroke unit after symptom onset or time last seen well [OR (95% CI) = [1.29 (1.23 to 1.35)], from admission to assessment by a stroke specialist [1.10 (1.06 to 1.14)] and from admission to assessment by a physiotherapist [1.16 (1.12 to 1.21)] were all independently associated with SAP. Short door to needle times were associated with lower odds of SAP [0.90 (0.83 to 0.97)].

4.2.4 Conclusion

Times from stroke onset and admission to certain key stroke care processes were associated with SAP. Understanding how timing of these care processes relate to SAP may enable development of preventive interventions to reduce antibiotic use and improve clinical outcomes.

4.3 Introduction

Stroke Associated Pneumonia (SAP) occurs in around 7-13% of patients during the first seven days of admission with a stroke (76). SAP is independently associated with worse functional outcomes, increased mortality and healthcare costs related to stroke care (41). Identification of potentially modifiable factors associated with SAP could ultimately lead to improved patient outcomes and reduce antibiotic use, which is a priority in an era of increasing antimicrobial resistance (112).

There are currently few strategies available to reduce the risk of SAP. Early swallow assessment and receipt of organised stroke unit care are associated with lower risk of SAP development (27, 72), yet little is known about how other care processes relate to risk of SAP. Preventive antibiotics have not been shown to reduce the risk of SAP or improve clinical outcomes. Other interventions, such as oral care and metoclopramide may reduce the risk of SAP, but require further evaluation (98, 104).

Better understanding the relationships between stroke care processes, their timing and the risk of SAP could provide a basis for interventions to improve patient outcomes and antibiotic stewardship. The main aim of this study was therefore to investigate the associations between the timing of stroke care processes spanning pre-hospital, hyperacute and acute care and the development of SAP.

4.4 Methods

4.4.1 Study design

We undertook an observational cohort study using patient level data from the Sentinel Stroke National Audit Programme (SSNAP), for all confirmed and recorded strokes between the 1st of April 2013 and the 31st of December 2018 in England and Wales. Stroke units with fewer than 150 stroke admissions per year were excluded from the study, in order to focus on specialist stroke units and not on those repurposed for occasional patients (142).

4.4.2 Data source

SSNAP is a mandatory stroke registry implemented in 2013 by the Intercollegiate Stroke Working

Party. It records baseline characteristics, demographic details and stroke care information in order to

facilitate continued quality improvement of stroke care across England, Wales and Northern Ireland

(53). The Healthcare Quality Improvement Partnership (HQIP) governs SSNAP, and made the final

approval of the data transfer. Data access requests should be directed to HQIP.

4.4.3 Clinical characteristics

We extracted baseline patient characteristics as previously described (142), including the following

vascular and SAP risk factors: age on admission, sex, total baseline National Institutes of Health

Stroke Scale (NIHSS) score, pre-stroke modified Rankin Scale (mRS) score, diabetes, atrial fibrillation

(AF), hypertension, congestive heart failure, previous stroke or transient ischaemic attack (TIA) and

presence of dysphagia.

4.4.4 Stroke care phases and processes

As SAP occurs most often during the first 72h of admission(76), we focused on stroke care processes

during the pre-hospital, hyperacute and acute phases of the stroke pathway. A stroke care process

was defined as a time to event variable, i.e the time it took the patient from a specific event to

receiving the specified care. We categorised time into quartiles to avoid distributional issues with

outliers and allow interpretable incorporation of 'unrecorded' and 'not applicable' categories in our

analysis. The selected stroke care processes included time from symptom onset or time last seen

well to arrival at stroke unit, time from arrival at hospital to be assessed by a stroke nurse or to have

a swallow assessment, time from arrival at hospital to receiving thrombolysis (door-to-needle time),

time from arrival at hospital to be assessed by a stroke specialist doctor and time from arrival at

hospital to be assessed by a physiotherapist (up to 72 hours from admission). As swallow screens are

generally performed by the stroke assessment nurse, there was high collinearity between the two

processes. We created the aforementioned care process to address this collinearity. We selected

these care processes after preliminary analysis of the data, discussions with the SSNAP team,

consideration of data availability and discussions with a stroke specialist paramedic with experience

of SSNAP data extraction and analysis. In all of our care process categories, with the exception of

thrombolysis, the first quartile was selected as the reference. For thrombolysis, those patients who

did not receive thrombolysis were selected as the reference category. We modelled thrombolysis

differently, because the process of thrombolysis incorporates additional time-limited processes

compared to patients that do not undergo thrombolysis, such as expedited CT scanning and

assessments to facilitate optimal door-to-needle time.

4.4.5 Statistical analysis and data structure

The primary outcome measure was SAP defined here within SSNAP as new antibiotic initiation for

suspected pneumonia started within the first 7 days of admission. The data had a hierarchical

structure with stroke patients clustered within stroke units. A mixed-effects logistic regression

modelled the binary presence of SAP vs no-SAP. The care processes for both SAP and non-SAP

patients were described using standard descriptive statistics. Clinical characteristics and stroke care

processes were modelled as fixed effects with stroke unit modelled as the random intercept. We

modelled each care process individually with the clinical characteristics and then modelled each care

process based on VanderWeele's principals of confounder selection to avoid adjusting for factors

thought to be on the causal pathway (133). A sensitivity analysis was performed for all patients

whose length of stay was 7 days or more to ensure there was no misclassification due to the time

component associated with the definition of SAP in our study. Odds ratios (ORs) and 95% confidence

intervals (CIs) are reported. All statistical analysis was performed in Stata v.14 IC.

4.5 Results

The dataset comprised 456,590 patients across 322 units. After excluding the units with fewer than

150 stroke admissions per year, the final dataset comprised 413,133 patients across 169 stroke

units. SAP was recorded in 34,987 (8.5%) patients. A full description of the clinical characteristics is

presented in Table S1. The median time from symptom onset to arrival at a stroke unit was 7.35

hours (IQR 4.20 – 20 hours). A total of 47,240 patients (11.4%) received thrombolysis, comprising 42,117 (89.2%) non-SAP patients and 4618 (9.8%) SAP patients. The median time from arrival at hospital to be seen by a stroke specialist doctor was 11.6 hours (IQR 2.0 -20.3 hours). A full description of the times and cut-offs based on quartiles can be found in Table 4.4.1.

The analysed sample comprised of 389,626 patients across 169 stroke units after also accounting for missing data for SAP and dysphagia (Figure 4.4.1).

For pre-hospital care, the patients who arrived at the stroke unit within the third and fourth quartiles was independently associated with SAP (OR of 1.1, 95% CI 1.0 – 1.1 and OR of 1.2, 95% CI 1.2 – 1.3, respectively) (4.4.2). Patients with door to needle time in the first and second quartile were associated with decreased odds of SAP, with an OR of 0.89 (95% CI 0.82 to 0.96) in the first quartile and an OR of 0.94 (95% CI 0.87 to 1.0) in the second quartile. Patients who were assessed by a stroke specialist doctor in the fourth quartile had an increased odds of SAP with an OR of 1.1 (95% CI 1.0 – 1.1). Patients who were assessed by a physiotherapist in the fourth quartile were associated with increased odds of SAP with an OR of 1.2 (95% CI 1.1 – 1.2).

In the sensitivity analysis, 186,633 (45.2%) patients who were discharged or died within the first 7 days were excluded across the dataset, leaving 231,277 patients with SAP in 33076 (14.3%). Our findings were comparable to our main analysis, indicating that SAP was minimally misclassified. A full description of the sensitivity analysis can be found in the supplemental material in Table 4.4.3.
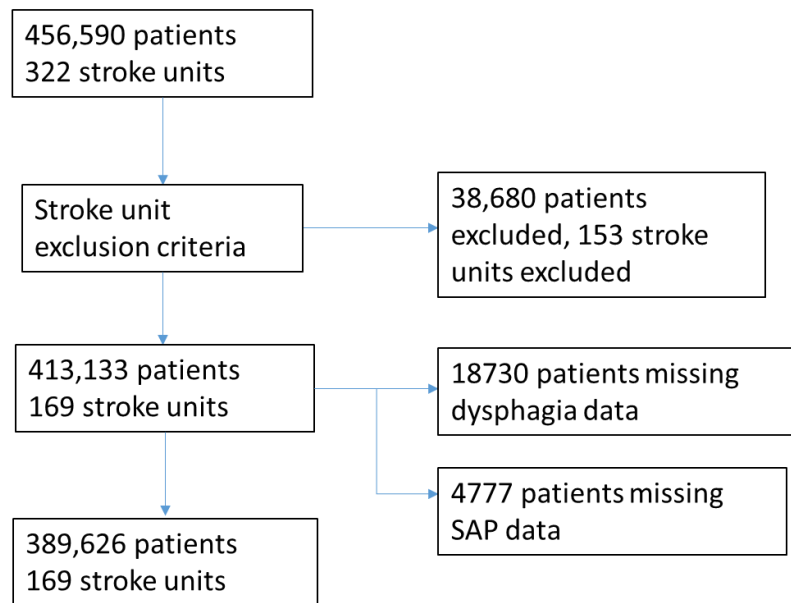
Figure 4.5.1. Flow diagram showing where patients were excluded and where patient data is missing to arrive at final sample size

CLINICAL CHARACTERISTIC	NON-SAP	SAP	MISSING
FEMALE	184734 (90.0%)	17980 (8.76%)	2524 (1.22%)
Age on arrival (y)			
<60	58604 (95.9%)	1846 (3.02%)	687 (1.12%)
60-69	63839 (93.9%)	3395 (4.99%)	741 (1.09%)
70-79	102229 (91.4%)	8397 (7.51%)	1182 (1.05%)
80-89	114011 (87.5%)	14646 (11.2%)	1571 (1.20%)
>90	39463 (84.3%)	6713 (14.3%)	596 (1.27%)
Ethnicity			
White	337526 (90.4%)	31889 (8.53%)	4118 (1.10%)
Asian	10919 (92.1%)	756 (6.38%)	177 (1.49%)
Black	4617 (93.7%)	252 (5.11%)	60 (1.21%)
Mixed	1272 (90.5%)	110 (7.82%)	24 (1.71%)
Other	23812 (90.9%)	1980 (7.56%)	398 (1.52%)
CHF	19022 (85.2%)	2986 (13.4%)	306 (1.37%)
Hypertension	202701 (90.3%)	19232 (8.57%)	2432 (1.08%)
Diabetes	78158 (90.4%)	7390 (8.54%)	933 (1.07%)
Atrial fibrillation	71285 (86.0%)	10501 (12.7%)	1056 (1.27%)
Previous stroke or TIA	99885(89.9%)	10029 (9.03%)	1196 (1.08%)
Stroke subtype			
Ischaemic stroke	333119 (90.9%)	29460 (8.04%)	3863 (1.05%)
ICH	42272 (87.3%)	5321(11.0%)	814 (1.68%)
mRS BEFORE STROKE			
0	212719 (93.1%)	13156 (5.76%)	2524 (1.11%)
1	57772 (90.4%)	5439 (8.51%)	680 (1.06%)
2	38017 (87.9%)	4765 (11.0%)	485 (1.12%)
3	41547 (85.4%)	6531 (13.4%)	581 (1.20%)
4	21678 (83.6%)	3898 (15.0%)	360 (1.39%)
5	6413 (82.7%)	1198 (15.4%)	147 (1.89%)
NIHSS ON ARRIVAL (MEDIAN, IQR)	4 (2 -9) n=330710	14 (6 - 20) n= 27800	-
DYSPHAGIC	14394 (32.4%)	27405 (61.7%)	2614 (5.89%)

Table 4.5.1. Summary data of clinical characteristics. TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, ICH – Intracerebral haemorrhage

STROKE CARE PROCESS	NON-SAP	SAP	MISSING
TIME FROM SYMPTOM ONSET TO ARRIVAL AT STROKE UNIT			
1ST QUARTILE (<4.20 HRS)	61033 (89.7%)	6274 (9.22%)	768 (1.12%)
2ND QUARTILE (4.20-7.35 HRS)	61603 (90.0%)	6157 (9.00%)	716 (1.04%)
3RD QUARTILE (7.35-20 HRS)	62382 (91.4%)	5239 (7.68%)	599 (0.88%)
4TH QUARTILE >20 HRS	62632 (91.4%)	5277 (7.70%)	588 (0.86%)
UNKNOWN TIME	130496 (90.2%)	12040 (8.32%)	2106 (1.46%)
DID THE PATIENT RECEIVE THROMBOLYSIS			
NO	4418 (87.7%)	422 (8.37%)	200 (4.00%)
NO BUT*	331611 (90.8%)	29947 (8.20%)	4072 (1.11%)
YES	42117 (89.2%)	4618 (9.78%)	505 (1.01%)
DOOR TO NEEDLE TIME			
1ST QUARTILE (<40 MIN)	9732 (90.5%)	943 (8.77%)	74 (0.69%)
2ND QUARTILE (40-50 MIN)	9694 (89.4%)	1048 (9.67%)	98 (0.90%)
3RD QUARTILE (50-80 MIN)	10026 (88.7%)	1139 (10.0%)	134 (1.28%)
4TH QUARTILE (>80 MIN)	9858 (88.7%)	1098 (9.87%)	164 (1.57%)
TIME FROM ARRIVAL AT HOSPITAL TO BE ASSESSED BY A STROKE NURSE OR HAD A SWALLOW SCREEN (COMPOSITE)			
1ST QUARTILE (<10 MIN)	30553 (90.1%)	2993 (8.82%)	373 (1.10%)
2ND QUARTILE (10-90 MIN)	76567 (91.3%)	6550 (7.81%)	721 (0.86%)
3RD QUARTILE (90 – 260 MIN)	63345 (91.6%)	5289 (7.64%)	551 (0.79%)
4TH QUARTILE (>260 MIN)	73827 (92.0%)	5700 (7.10%)	711 (0.89%)
UNKNOWN TIME	133854 (88.8%)	14455 (9.60%)	2415 (1.60%)
TIME FROM ARRIVAL TO BE ASSESSED BY A STROKE SPECIALIST DOCTOR			

1ST QUARTILE (<2HRS)	87457 (90.2%)	8563 (8.83%)	959 (0.99%)
2ND QUARTILE (2-11.6 HRS)	88546 (90.7%)	8130 (8.32%)	952 (0.98%)
3RD QUARTILE (11.6 – 20.3 HRS)	89125 (91.6%)	7125 (7.32%)	984 (1.01%)
4TH QUARTILE (>20.3 HRS)	87979 (90.3%)	8438 (8.67%)	1017 (1.04%)
UNKNOWN TIME	25021 (87.4%)	2731 (9.54%)	865 (3.02%)
TIME FROM ARRIVAL TO BE ASSESSED BY A PHYSIOTHERAPIST			
1ST QUARTILE (<15.6 HRS)	79006 (90.9%)	7171 (8.25%)	771 (0.89%)
2ND QUARTILE (15.6 – 21.3 HRS)	79951 (92.0%)	6173 (7.11%)	754 (0.87%)
3RD QUARTILE (21.3 – 27.8 HRS)	79502 (91.2%)	6879 (7.07%)	808 (0.93%)
4TH QUARTILE (>27.8HRS)	78015 (89.6%)	8266 (9.50%)	818 (0.94%)
UNKNOWN TIME	61672 (88.4%)	6498 (9.31%)	1626 (2.33%)

Table 4.5.2. Summary data of stroke care processes and criteria used in SSNAP and included in the model. *No but category means the patient did not received thrombolysis due one of the following reasons: the patient arrived outside the thrombolysis window, associated co-morbidity, use of contraindicated medication, refusal of thrombolysis by the patient, age, the symptoms were improving, stroke either too mild or too severe, symptom onset time was unknown or for some other medical reason

Stroke Care Process	Odds ratio (individual care process)	95% Confidence Interval	Odds ratio (VanderWeele confounder selection)	95% Confidence Interval
Time from symptom onset to arrival at stroke unit				
1st quartile (<4.20 hrs)	1.0 (reference)	-	1.0 (reference)	-
2nd Quartile (4.20-7.35 hrs)	1.06	1.02 to 1.10	1.06	1.0 to 1.10
3rd Quartile (7.35-20 hrs)	1.12	1.07 to 1.16	1.12	1.07 to 1.16
4th Quartile (>20 hrs)	1.29	1.23 to 1.35	1.29	1.23 to 1.35
Unknown	1.14	1.10 to 1.18	1.14	1.10 to 1.18
Time from arrival at hospital to be assessed by a stroke nurse or have a swallow screen (composite)				
1st quartile (<10 min)	1.0	-	1.0 (reference)	-
2nd quartile (10-90 min)	0.96	0.92 to 1.0	0.96	0.92 to 1.01
3rd quartile (90 – 260 min)	0.97	0.93 to 1.0	0.97	0.92 to 1.02
4th quartile (>260 min)	1.0	0.96 to 1.1	0.99	0.93 to 1.03
Unknown	1.1	1.0 to 1.1	1.04	0.99 to 1.10
Door to needle time				
Did not receive thrombolysis	1.0 (reference)	-	1.0 (reference)	-
1st quartile (<40 min)	0.83	0.76 to 0.89	0.90	0.83 to 0.97

2nd quartile (40-50 min)	0.87	0.82 to 0.94	0.95	0.88 to 1.02
3rd quartile (50-80 min)	0.94	0.88 to 1.0	1.02	0.95 to 1.10
4th quartile (>80 min)	1.0	0.94 to 1.1	1.06	0.99 to 1.14
Time from arrival to be assessed by a stroke specialist doctor				
1st quartile (<2hrs)	1.0	-	1.0 (reference)	-
2nd quartile (2-11.6 hrs)	1.1	1.0 to 1.1	1.02	0.99 to 1.06
3rd quartile (11.6 – 20.3 hrs)	1.1	1.0 to 1.1	1.01	0.97 to 1.05
4th quartile (>20.3 hrs)	1.2	1.1 to 1.2	1.10	1.06 to 1.14
Unknown	1.0	0.96 to 1.1	0.91	0.86 to 0.96
Time from arrival to be assessed by a physiotherapist				
1st quartile (<15.6 hrs)	1.0 (reference)		1.0 (reference)	-
2nd quartile (15.6 – 21.3 hrs)	0.97	0.94 to 1.01	0.96	0.93 to 1.00
3rd quartile (21.3 – 27.8 hrs)	1.0	0.97 to 1.04	0.98	0.95 to 1.02
4th quartile (>27.8hrs)	1.2	1.2 to 1.3	1.16	1.12 to 1.21
Unknown	0.83	0.79 to 0.86	0.79	0.75 to 0.82

Table 4.5.3. Multivariable multilevel logistic regression Odds ratios for stroke care processes describing their association with SAP. VanderWeele confounder selection for each care process (clinical characteristics were selected in all care processes) – 1. arrival at stroke unit – clinical characteristics /2. assessment by a stroke nurse or swallow screen –arrival to stroke unit/3. door to needle time –arrival at stroke unit/ 4.assessment by stroke specialist doctor –arrival at stroke unit and assessment by a stroke

nurse or swallow screen/5.assessment by physiotherapist – arrival at stroke unit, assessment by a stroke nurse or swallow screen and assessment by a stroke specialist doctor.

Stroke Care Process	Odds ratio (VanderWeele confounder selection)	95% Confidence Interval
Time from symptom onset to arrival at stroke unit		
1st quartile (<4.20 hrs)	1.0 (reference)	-
2nd Quartile (4.20-7.35 hrs)	1.03	0.99 to 1.08
3rd Quartile (7.35-20 hrs)	1.07	1.02 to 1.12
4th Quartile (>20 hrs)	1.17	1.12 to 1.23
Unknown	1.06	1.02 to 1.09
Time from arrival at hospital to be assessed by a stroke nurse or have a swallow screen (composite)		
1st quartile (<10 min)	1.0 (reference)	-
2nd quartile (10-90 min)	0.96	0.91 to 1.01
3rd quartile (90 – 260 min)	0.97	0.92 to 1.02
4th quartile (>260 min)	0.97	0.92 to 1.03
Unknown	0.94	0.90 to 1.00
Door to needle time		
Did not receive thrombolysis	1.0 (reference)	-
1st quartile (<40 min)	1.00	0.92 to 1.09
2nd quartile (40-50 min)	1.02	0.95 to 1.11
3rd quartile (50-80 min)	1.10	1.02 to 1.18
4th quartile (>80 min)	1.14	1.06 to 1.23
Time from arrival to be assessed by a stroke specialist doctor		

1st quartile (<2hrs)	1.0 (reference)	-
2nd quartile (2-11.6 hrs)	1.03	0.99 to 1.07
3rd quartile (11.6 – 20.3 hrs)	1.04	1.00 to 1.09
4th quartile (>20.3 hrs)	1.08	1.04 to 1.13
Unknown	0.81	0.77 to 0.86
Time from arrival to be assessed by a physiotherapist		
1st quartile (<15.6 hrs)	1.0 (reference)	-
2nd quartile (15.6 – 21.3 hrs)	0.98	0.93 to 1.02
3rd quartile (21.3 – 27.8 hrs)	0.98	0.94 to 1.02
4th quartile (>27.8hrs)	1.04	1.0 to 1.08
Unknown	0.71	0.67 to 0.74

Table 4.5.4 Sensitivity analysis results. All care processes were included in sensitivity analysis model as described as in original model

4.6 Discussion

We found that those patients with longer times to arrival at a stroke unit, assessment by a stroke specialist doctor and assessment by a physiotherapist were independently associated with up to 30% increased odds of SAP for those above the median on each of these care process measures. We also found that shorter time to thrombolysis was associated with reduced odds of SAP. Whilst we cannot conclude causal relationships, there are plausible mechanisms that warrant exploration. These findings are of interest as they highlight components of the pre-hospital, hyperacute and acute care pathway, and delays in receiving them, could be important targets for interventions to reduce the risk of SAP.

Increased times to arrival at a stroke unit were associated with increased odds of SAP, independent of the other care processes and baseline characteristics such as age and stroke severity. Whilst we cannot exclude that shorter time to arrival at a stroke unit was a marker of more rapid stroke care after arrival,

there could be several other potential explanations. Faster dispatch times could reduce the likelihood of aspiration, by reducing the "the time down" and by expediting interventions such as positioning (42, 61) and thrombolysis or thrombectomy. Conversely, we cannot exclude that some patients with later dispatch times already had evolving pneumonia which manifest clinically after arrival in hospital (143).

Previous studies have found that thrombolysis reduces the risk of SAP and that SAP is associated with worse outcomes in thrombolysed patients (139). We additionally found that door to needle time within 40 minutes was independently associated with reduced odds of SAP. However, there appears to be no difference in development of incident pneumonia between placebo and tissue plasminogen activator treated patients in randomised trials (144, 145). Our findings in real-world practice could be explained by early improvement in stroke severity (including level of alertness and dysphagia) in those with faster door to needle times. Another possible explanation is that immunosuppression induced by thrombolysis with tissue plasminogen activator, might potentially increase the susceptibility to SAP with treatment later rather than earlier in the thrombolysis time window (146, 147).

Delays in physiotherapy assessment and delays to assessment by a stroke specialist doctor were also associated with increased odds of SAP, independent of each other and the other care processes evaluated. As many patients develop SAP within the first 24 hours (76), later assessment by the stroke specialist doctor could be a marker for late diagnosis of SAP and decision-making on antibiotic initiation. Another factor is that a stroke specialist would influence various other aspects of hyperacute and acute management such as thrombolysis or thrombectomy which could affect the odds of developing SAP. Physiotherapy interventions such as turning and mobilization and chest physiotherapy may reduce the risk of pneumonia in stroke (101, 148). However, we did not have access to any data detailing specific physiotherapy interventions in individual patients. Shorter times to assessment by a physiotherapist could facilitate earlier mobilisation and positioning although there appears to be no data to support this from randomised trials (102, 149).

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We cannot exclude the possibility of reverse causality in our findings. For example, patients with evolving or diagnosed with SAP could be more unwell, leading to delays in certain assessments e.g. by physiotherapy, or requiring longer at-scene assessments by the paramedics, leading to delayed or longer transfers to the stroke unit (41).

Our results needs to be interpreted with caution. Firstly, the inclusion of unknown times in each stroke care process has implications for interpretation. The unknown time to event for symptom onset to arrival at the stroke unit, time to be assessed by a stroke nurse, time to be assessed by a stroke specialist doctor, and time to be assessed by a physiotherapist indicated statistically significant results. This means interpretation of the other timing categories, as the relationship reported between time to event metrics and outcome could be biased if unknown time is not randomly distributed. Unknown time to arrival at a stroke unit could be associated with SAP if the patient experienced a milder stroke, delaying access to hospital, being diagnosed, or simply causing an arrival without a clear time of onset. This uncertainty could then impact upon time to be assessed by a stroke nurse. The decreased odds of SAP in the unknown time to be seen by a physiotherapist needs to be considered separately. Time to be seen by a physiotherapist is measured in SSNAP only if they were seen within 72 hours from admission. If a patient was discharged, due to good health or death, before being seen by a physiotherapist, it could provide an explanation as to our results.

Our findings, if confirmed, would strengthen existing evidence for good quality and timely stroke care. Previous studies have suggested that timing of dysphagia assessment is also associated with development of SAP (72, 73). Considering how the timings of certain care processes in the pre-hospital, hyperacute and acute phase relate to SAP could lead to the development of interventions that can reduce the incidence of SAP and implications for antibiotic stewardship. Variation in the timings of care processes could also be a modifiable contributor to the observed variation in SAP frequency (36) and therefore merits further research.

Our study has several strengths and limitations. The SSNAP data contains unselected patient data with a high case-ascertainment providing generalizable findings that are representative of real-world events. Our observations for care process timing are likely to be relevant to stroke care beyond the UK. However, the lack of complete data for each of the stroke care processes across our dataset is a limiting factor. The data may be missing for reasons related to prognosis, which limits the conclusions that can be drawn from our study. In addition, the categorisation of these continuous measures of time might increase the presence residual confounding. We were not able to include other potentially important stroke care processes that could be associated with SAP, such as time to CT scan or the amount of physiotherapy time each patient received. While these data are available to extract from SSNAP, we did not have access to this at the time of this study. It is also important to highlight that there are unmeasured aspects of stroke care which could provide further insight. Finally, we were not able to account for organisational level factors, such as staffing levels, stroke unit size or geography. Organisational level factors may have been important confounders as they may represent directly or indirectly measures for the quality of care the stroke patients received.

4.7 Conclusion

Increased time from symptom onset to arrival, thrombolysis door to needle time, time to be seen by a physiotherapist and time to be seen by a stroke specialist doctor were associated with increased odds of SAP even once measures of patient, stroke, and prior care process characteristics had been adjusted. Better understanding how the timing of these care processes relate to SAP may enable development of preventive interventions to reduce antibiotic use and improve clinical outcomes

Chapter 5 - How do clinicians approach diagnosis and antibiotic initiation in stroke- associated pneumonia? A UK cross-sectional study

5.1 Preface

In the previous chapter, I evidenced that there are specific care processes that have an association with the development of SAP. However, since the variable SAP in my thesis is based on SSNAP's definition of SAP (antibiotic initiation for suspected SAP within the first 7 days of stroke admission), it is important to find out what leads clinicians to initiate antibiotics. This way, I try to balance the ambiguity of the definition of SAP in SSNAP and attempt to gain insight into other possible answers to the observed variation of SAP in chapter 3.

5.2 Abstract

5.2.1 Introduction

Stroke associated pneumonia (SAP) is a common complication in stroke unit care. However, diagnosis of SAP is not standardised and little is known about how clinicians approach antibiotic initiation. Exploring how clinicians treat SAP with antibiotics is important and potentially provides insight into the observed variation of SAP prevalence across the UK.

5.2.2 Methods

We undertook a UK cross-sectional survey in which we presented four different clinical scenarios of suspected SAP and asked the participating clinicians if they would initiate antibiotics or not, either as the scenario was presented or after adjustment of scenario characteristics. The Pneumonia In Stroke ConsEnsuS (PISCES) Group criteria for SAP were used to develop each scenario, using clinical factors, laboratory investigations and chest X-ray findings. Interrater agreement for antibiotic initiation as the scenario was initially presented was calculated using Fleiss's Kappa test.

5.2.3 Results

Of the 86 participants who started the survey, 45 (52%) completed it. The number of participants that would initiate antibiotics as the patient was described in each scenario were 66/67 (99%), 25/55 (45%), 11/53 (21%) and 15/47 (32%) respectively. The characteristics with the most diverse threshold levels included C-reactive protein, white blood cell count and respiratory rate. The calculated kappa value for all participants was 0.39, suggesting minimal agreement among clinicians for antibiotic initiation.

5.2.4 Conclusions

Our findings indicate variation is present between clinicians in the approach to antibiotic initiation for suspected SAP. Further research is needed to standardise diagnostic algorithms and determine the implications on antibiotic stewardship and patient outcomes.

5.3 Introduction

Stroke-associated pneumonia (SAP) occurs in around 13% of stroke survivors (76). It is associated with adverse outcomes including increased mortality, morbidity and in-hospital stay (41). When SAP is suspected, prompt antibiotic treatment is recommended (107). Antibiotic usage in clinical care settings has increased worldwide resulting in major concerns over antibiotic resistance and the long term impact on clinical outcomes from infections (112). Previous evidence has shown that variation in the prevalence of SAP is present between stroke units, and that patient demographics and clinical characteristics account for only a small proportion of this variation (35, 142). There is a need to identify what other factors could explain this observed variation as SAP variation could lead to antibiotic overuse. One key aspect is the decision-making behaviour of clinicians in suspected SAP. There is evidence to suggest that clinicians approach SAP diagnosis heterogeneously (108), and that diagnostic algorithms for pneumonia vary between guidelines (35, 150). The Pneumonia In Stroke ConsEnsuS (PISCES) Group has proposed operational terminology and a diagnostic algorithm, however these have not been validated and their role in informing antibiotic initiation is unclear (37). Better understanding of the different clinical factors and investigations, along with their corresponding thresholds, that clinicians use for antibiotic initiation is important in order to improve antibiotic stewardship and standardise treatment of SAP to avoid antibiotic overuse or under-treatment.

The aim of this study was to explore the clinical characteristics (including thresholds where applicable), used by clinicians in the UK when considering antibiotic initiation for suspected SAP.

5.4 Methods

5.4.1 Study design

We performed a cross-sectional survey of UK clinicians working in stroke care to assess their approach to diagnosis and antibiotic initiation for suspected SAP. The survey consisted of four case scenarios of varying SAP ambiguity, summarised in **Table 5.1**, based on the PISCES criteria for diagnosis (9). Scenario 1 contained a patient with features of definite SAP, whereas the following three scenarios changed patient characteristics, stroke characteristics, symptoms, signs and investigation results so that probable or definite PISCES criteria were not met. In each scenario, if antibiotics were not initiated, respondents were offered additional options which further modified symptoms, signs, or investigations (including thresholds where applicable) and asked if they wanted to reconsider their initial decision regarding antibiotic initiation.

Based on the PISCES SAP diagnostic criteria and additional factors of perceived importance, the scenarios included clinical characteristics: age, stroke severity (NIHSS score) and subtype; symptoms and signs: respiratory rate (RR), cough, temperature, oxygen saturations (%), dysphagia and chest crackles; clinical investigations: C-reactive protein (CRP), partial pressure of oxygen (PaO2) values, white blood cell (WBC) count and chest x-ray. Age was divided into 4 different thresholds: <60 years, between 61 – 75 years of age, between 76-85 years of age and >85 years of age. Stroke severity was divided into 4 different thresholds: NIHSS <4, NIHSS 5-15, NIHSS 16-20, NIHSS >21. RR was also divided into thresholds into <18 breaths/minute (bpm), 18-22 bpm, 22-25 bmp, >25bpm. CRP thresholds were <10 mg/L, 11-50 mg/L, 51-75 mg/L, >75 mg/L. WBC thresholds were $<4.0 \times 10^9$/L, $4.1-11.0 \times 10^9$/L, $11.1-17.0 \times 10^9$/L, $>17.1 \times 10^9$/L. PaO2 thresholds were 100-95 mmHg, 94-85 mmHg, <85mmHg. O2 saturation thresholds were 100-96%, 95-93%, 92-89%, <88%. Temperature thresholds were <37 degrees Celsius, 37.1-38 degrees Celsius, 38.1-38.5 degrees Celsius and >38.5 degrees Celsius. Chest x-ray changes were provided

as either having no abnormalities or changes consistent with infection. The survey participants had the

option of multiple choice for each response per component of the scenario. In addition to the previous

values, the option of 'not relevant to the decision to initiate antibiotics' was also offered for each

variable

	Patient age	Stroke subtype	NIHSS	Temperature	Respiratory rate	Crackles	Cough	Chest x-ray	PaO2/O2 sat	Lab findings	Additional information
Scenario 1	73	TACI	16	38.5°C	26/minute	Unilateral	Purulent	Unilateral infiltrates	85 mmHg	CRP 75mg/L	NA
Scenario 2	55	LACI	11	38°C	20/minute	NA	Non-purulent	No abnormalities	NA	CRP 25mg/L	NA
Scenario 3	93	POCI	5	36.5°C	17/minute	Unilateral	Non-purulent	No abnormalities	NA	WBC 10.7x10^9/L	NA
Scenario 4	85	TACI	21	37°C	20/minute	NA	NA	No abnormalities	92% room air	CRP 75mg/L	Dysphagic by SLT

Table 5.4.1. Description for each of the scenarios in our study. TACI – total anterior circulation infarct, NIHSS – National institute of health stroke scale, PaO2 – Oxygen arterial pressure, CRP – C-reactive protein, LACI – lacunar infarct, POCI – posterior circulation infarct, WBC – white blood cell count, SLT – Speech and Language therapist

Information asked of survey participants included profession, hospital location (135) and years of experience since qualifying (136). The study was considered by the ethics committee of the Division of Cardiovascular Sciences at the University of Manchester, but no ethical approval was required. The survey was developed using Select Survey software and piloted twice with three consultant stroke physicians at Manchester Centre for Clinical Neurosciences, Salford Royal Hospital. Changes to the phrasing of the question and the scenarios were adopted accordingly after each round of piloting.

5.4.2 Data collection

The survey was distributed via social media, and directly to members of the British Association of Stroke Physicians (BASP) and NHS Getting It Right the First Time (GIRFT) network. Some overlap in membership was present between BASP and GRIFT due to their respective audiences. Both organizations distributed the survey via email twice, on the 1st of December 2019 and the 4th of January 2020. The survey was open to responses from 1st of December 2019 to 1st of February 2020. The survey was closed early due to lockdown measures and increased influence of the SARS-Cov-2 pandemic.

5.4.3 Data analysis

Descriptive statistics were calculated for the participant characteristics and clinical scenario responses. The level of agreement compared to random chance alone among participants for antibiotic initiation as the patient was described in each scenario was calculated using a multi-rater Kappa statistic. This was calculated overall and split for rater characteristics as consultants and non-consultants.

5.5 Results

The survey was started by 86 participants with 66 (77%) completing scenario 1, and 45 (52%) completing the survey in full. There were between 1 and 9 participants from each region of the UK (Scotland, Wales, Northern Ireland and the 15 Comprehensive Research Network (CRN) regions of England(151).) The CRN is a network of public and healthcare organizations who participate in high quality research and advancing knowledge in the UK. Of the 86 participants that started the survey, 74 (86%) were consultant level. The most common UK CRN regions were Scotland and Greater Manchester, each with 9 (10%) participants. The most common parent specialty mentioned by the participants was geriatrics, in (71%) participants.

In scenario 1 (**Table 5.4.1**), 67 of the 86 participants completed this scenario and 66 (99%) of the participants would initiate antibiotics as the patient was described. All 66 that initiated antibiotics initially would continue to initiate antibiotics in the absence of a cough, although 4 (6%) participants withheld antibiotics in the absence of crackles, 25 (37%) if a temperature of <37°C, and 9 (14%) if the chest x-ray was normal. Higher values of PaO2 prompted most participants to withhold antibiotics, with 20 (30%) if PaO2 was at 100-95 mmHg and 7 (10%) if PaO2 <85 mmHg. Participants considered lower CRP values as a reason to withhold treatment, with 37 (56%) withholding at <10 mg/L, compared with 9 (14%) participants that would withhold antibiotics at >75mg/L. Lower and normal WBC thresholds prompted clinicians to withhold antibiotics compared to higher levels, with 20 (30%) participants withholding antibiotics at WBC <4.0 x10^9 and 30 participants withholding at 4.1-11x10^9. The presence of dysphagia led one participant to withhold treatment. Patient age, stroke severity and dysphagia were not considered as major factor for participants to withhold or start treatment, with only 60, 62 and 65 participant considering the characteristic important for their decision of treatment. **Figure 5.5.1** shows a graphic description for each answer provided by all participants in scenario 1.

For the second scenario, as seen in **Table 5.4.1**, we decreased the patient age, stroke severity, the

CRP concentration and changed the chest x-ray to without abnormalities compared to scenario 1. In

this scenario, the PISCES diagnostic criteria for probable or definite SAP were not met, but 25 (45%)

of 55 participants would initiate antibiotics as the patient was described. Tachypnoea, increased

temperature, the presence of unilateral crackles and lower PaO2 values prompted the majority of

the remaining 30 participants to reconsider antibiotic treatment. Thresholds for RR varied, with 13

(43%) participants initiating antibiotics at a RR between 21-24/minute and 25 participants starting

treatment at a RR >24/minute. Increased CRP concentrations and increased WBC led participants to

reconsider antibiotic treatment. However, thresholds varied with 10 (33%) participants

reconsidering treatment at CRP concentrations between 26 – 50 mg/L, 26 (86%) participants

reconsidering treatment between 51-75 mg/L, 23 (76%) participants initiating antibiotics with WBC

between $11.1 – 17.0x10^9$/L and 25(83%) participants initiating antibiotics with WBC $>17.0x10^9$/L.

Chest x-ray findings consistent with infection also led 30 (100%) participants to reconsider antibiotic

treatment. The presence of dysphagia led 17 (56%) participants to reconsider treatment. Stroke

severity, increased age and stroke subtype were considered irrelevant to antibiotic initiation for

most participants. A graphic representation for antibiotic initiation vs no antibiotic initiation among

participants in scenario 2 can be seen in **Figure 5.5.2.**

In our third scenario (**Table 5.4.1**), we increased the patient age, decreased the stroke severity,

changed the stroke subtype, added a cough and unilateral crackles, and added WBC to the

investigations. In this scenario, 11 (21%) of 53 respondents would initiate antibiotics as the patient

was described, without meeting PISCES diagnostic criteria for probable or definite SAP. Increased

temperature, RR, CRP concentrations, WBC, chest x-ray changes consistent with infection prompted

the remaining 42 participants to reconsider antibiotic treatment. 9 (21%) participants would initiate

antibiotics with a RR between 19-22/minute and 38 (90%) with RR >22/minute. For CRP, 27 (64%)

participants would initiate antibiotics between 51-75 mg/L and 37 (88%) participants with CRP

>75mg/L. Dysphagia led 15 (35%) participants to reconsider antibiotic treatment. Stroke severity,

patient age and stroke subtype were considered irrelevant to their decision for antibiotic initiation. A graphic representation for antibiotic initiation vs no antibiotic initiation among participants in scenario 3 can be seen in **Figure 5.5.3.**

In our final scenario (**Table 5.4.1**), the most notable features were the presence of dysphagia and a CRP concentration of 75 mg/L, all other parameters mentioned were considered to be in the normal range. For this scenario, 15 (32%) of 47 participants would initiate antibiotics as the patient was described, and 32 withheld antibiotics. Similar to the previous scenarios, increased temperature, increased RR, presence of unilateral crackles, increased CRP concentrations, increased WBC, lower O2 saturation levels and changes in a chest x-ray consistent with an infection prompted a majority of participants to reconsider antibiotics. Varied thresholds for antibiotic initiation were comparable to scenario 2 and scenario 3, with a similar threshold for CRP and RR. Compared to the previous scenarios, O_2 levels had varied thresholds, with 20 (63%) initiating antibiotics between 91-89% and 30 (94%) participants initiating treatment at <88%. CRP had similar thresholds as seen in previous scenarios, with 8 (25%) participants reconsidering treatment between 51-75 mg/L and 30 (94%) participants starting treatment at >75mg/L. WBC had similar variability, with 14 (43%) participants starting treatment between $11.1-17.0x10^9$ and 30 (94%) participants starting antibiotics at $>17.0x10^9$. The absence of dysphagia in this scenario still led 11 (34%) participants to reconsider antibiotic treatment. Stroke severity, patient age and stroke subtype were considered irrelevant to their decision for antibiotic initiation. **Figure 5.5.4** shows a graphic representation for antibiotic initiation for scenario 4. A full breakdown of the most common threshold for each scenario can be seen in **table 5.5.1**.

The calculated Kappa value for agreement among consultants was 0.39 (95% Confidence Interval 0.05 – 0.56), while the calculated Kappa value among non-consultants was 0.49 (95% Confidence Interval -0.04 – 0.72). The calculated Kappa value for overall agreement for antibiotic initiation as the patient was described was 0.39 (95% Confidence Interval 0.002 – 0.44).

Scenario	Scenario 1 (n= 67)	Scenario 2 (n=55)	Scenario 3 (n=53)	Scenario 4 (n=47)
As the patient was described	66 (99%)	25 (45%)	11 (21%)	15 (32%)
Temperature (°C)	38.1 -38.5 (n=58)	>38 (n=29)	>38 (n=40)	>38 (n=32)
Cough	Yes (n=66)	Yes (n=3)	No antibiotic initiation (n=42)	Yes (n=6)
Crackles	Yes (n=62)	Yes (n=23)	Yes (n=1)	Yes (n=15)
Chest x-ray changes of infection	Yes (n=57)	Yes (n=30)	Yes (n=37)	Yes (n=31)
PaO2/O2 saturation	<85mmHg (n=59)	<85mmHg (n=26)	<85mmHg (n= 38)	<88% (n= 30)
CRP (mg/l)	51-75 and >75 (n=57)	>75 (n=25)	>75 (n=37)	>75 (n=30)
Respiratory rate (/minute)	>26 (n=56)	>24 (n=25)	>22 (n=38)	>22 (n=31)
WBC (x10^9/L)	11.1 – 17.0 (n=60)	>17.0 (n=25)	>17.0 (n=37)	>17.0 (n=30)
Dysphagia	Yes (n=65)	Yes (n=17)	Yes (n=11)	Yes (n=36)

Table 5.5.1. Table summarising the most common threshold for antibiotic initiation for participants that

did not initiate antibiotics as the patient was described in each scenario

Scenario 1
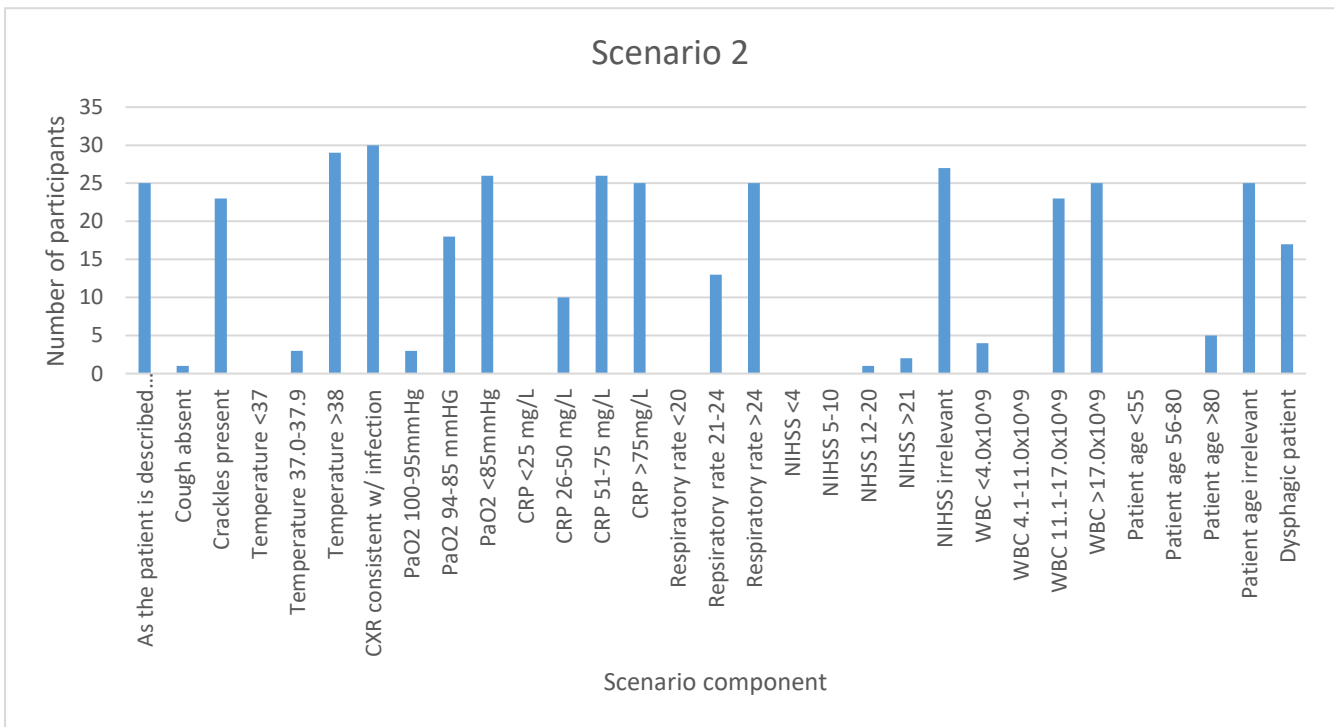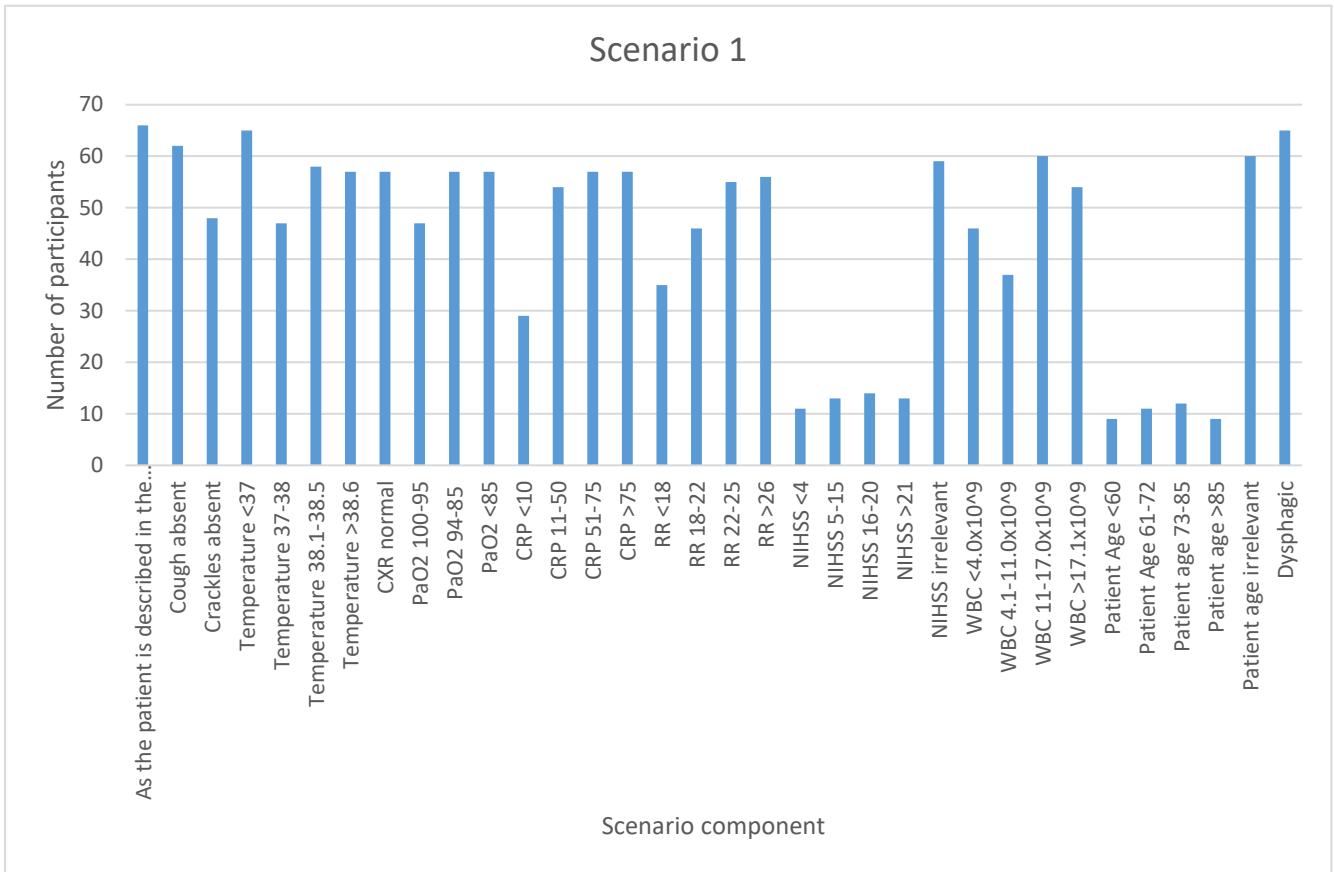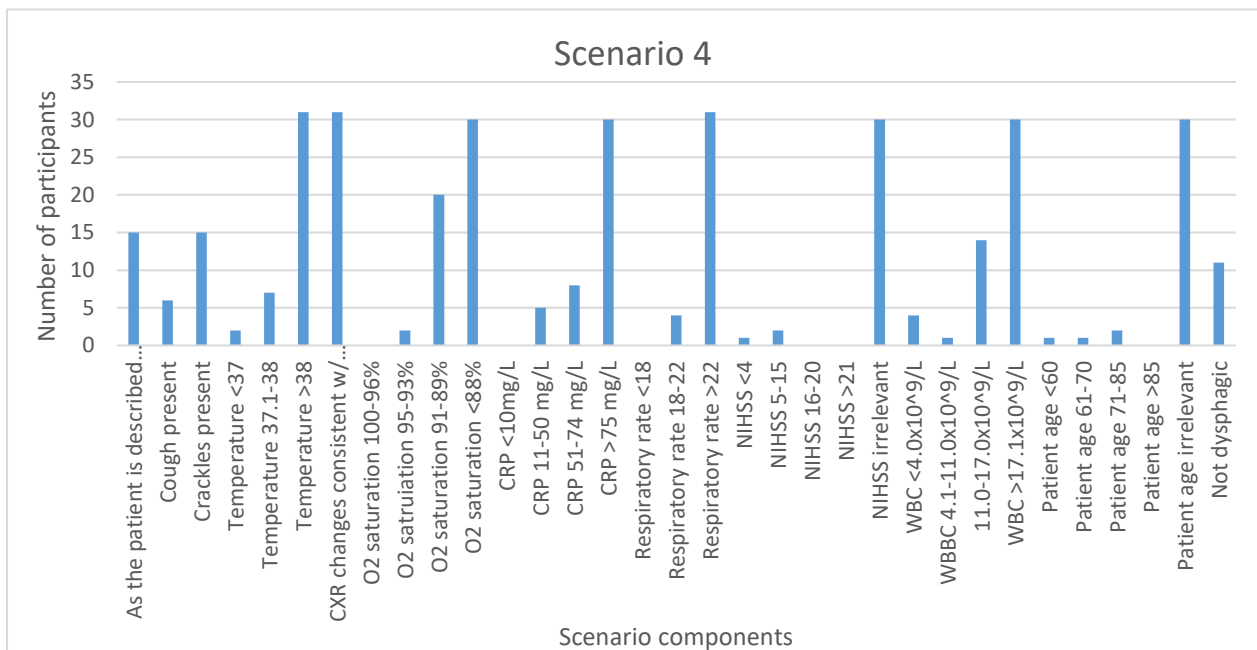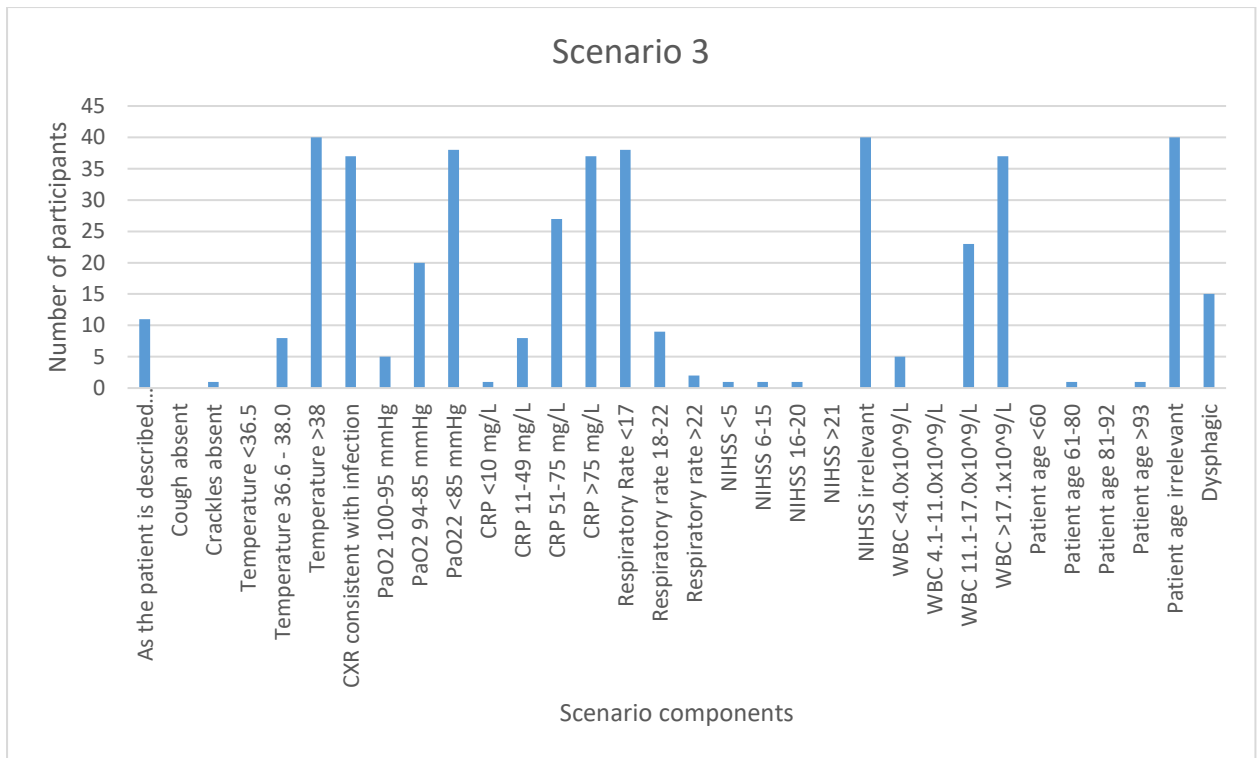
Scenario 2

Figures 5.5.1-5.5.4. Progressive bar charts showing the number of participants that would change their mind according to each possible answer in each scenario.

5.6 Discussion

Our findings indicate that chest x-ray changes consistent with infection, increased CRP levels, increased RR, or low PaO2/Sat O2 levels were associated with antibiotic initiation. Although these factors for suspected SAP are unsurprising, our findings show substantial variation in the threshold values applied, and initiation of antibiotics commonly in scenarios which did not meet the PISCES criteria for definite or probable SAP. However, we found no evidence that clinical decision making was affected by patient age, stroke severity or stroke subtype, all of which are known risk factors for SAP.

Our findings suggest that the majority of survey participants would initiate antibiotics in thresholds not comparable to the PISCES guidelines for SAP treatment (107). Among these characteristics, there were different thresholds that are important to highlight and could provide an important insight into clinician behaviour. CRP and WBC values were considered in all scenarios as important factors for antibiotic initiation. While values above 75mg/L in CRP and above 17.0×10^9/L in WBC were the most common indicators for antibiotic reconsideration, there was a significant proportion of participants that would reconsider antibiotics at a lower threshold, with the most common values being 51-75 mg/L in CRP and 11.1-17.0×10^9/L for WBC. Our findings suggest that clinicians, when approaching SAP and WBC values, seem to align with PISCES criteria, as WBC $>12.0 \times 10^9$/L are an important factor for the diagnosis of definite SAP in said criteria. CRP is important to highlight, as it is not a criterion in the PISCES criteria but it has been associated with increased diagnostic accuracy in the absence of pyrexia, with a threshold of $\geq$30mg/L (106, 152). It is also important to highlight that among all the participants, there were a proportion that would still initiate antibiotics at normal levels of these inflammatory biomarkers. This wide range of thresholds is important to highlight, as they suggest possible explanations for the variation in treatment for SAP (142). However, its interpretation needs to be done with caution. Reasons for this wide range of thresholds for suspected SAP are still unclear, with potential explanations including lack of uptake by practicing

clinicians, lack of detail in stroke guidelines or lack of familiarity between clinicians and the existing evidence.

Stroke severity, dysphagia and increased age have been consistently associated with increased SAP risk development (38, 43, 61), but these were not considered relevant for antibiotic initiation for the majority of participants. It is important to make the distinction between diagnostic and risk factors for SAP. We incorporated these risk factors to determine if they influenced clinician judgement. Our results indicated that clinicians do not use SAP risk factors as diagnostic factors to initiate antibiotics, at least in isolation.

Antibiotic initiation had varied thresholds across the different clinical characteristics. A cough was not considered as important as RR or crackles, however it is important to note that coughing in stroke patients is usually impaired (99). Compared to the other respiratory characteristics, tachypnoea had a higher rate of antibiotic initiation. While tachypnoea is not a specific sign for pneumonia, it is generally associated with pulmonary distress or a more clinically compromised patient, which makes our findings compatible with common medical practice (153). However, crackles, an expected finding in physical examination for a patient with pneumonia, was not deemed that important for antibiotic initiation for our participants compared to other clinical signs. While crackles are not a specific sign for pneumonia (154), there were no indications or signs for any of the other possible causes for crackles in our scenarios. This finding does raise the question regarding how much clinicians rely on physical examination findings for their diagnosis, with a possibility of over-reliability on laboratory findings and radiological findings.

Another important highlight of our study is the use of chest x-ray as a diagnostic tool, as the option of changes consistent with infection on chest x-ray was associated with initiation of antibiotic treatment in a majority of participants in all scenarios. This is important as there is evidence to suggest that chest x-rays have limited diagnostic value when compared to chest CT when diagnosing

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SAP, as chest x-ray has poor sensitivity at detecting SAP (78). Reliance on the presence of findings suggestive of infection on chest x-rays could contribute to could lead to antibiotic underuse.

Our findings can be compared to the study in German stroke units in two important aspects: stroke severity and chest x-ray use (138). In the study published by Harms et al, their findings suggested that clinicians in Germany view stroke severity as an important factor for antibiotic use. Our findings suggest that participants included in our study do not consider stroke severity as an important characteristic for antibiotic initiation. Possible explanations for this differences could include the way the authors presented their scenarios, as well as the options they presented. We included the option of "not relevant to antibiotic initiation", which could have influenced our participants. Another possible explanation for this difference could also be the differences among individual country practices and the time difference between the 2 studies was conducted, as new guidance has emerged in the 7 years between the studies. Another important factor they found was the use of chest x-rays for the diagnosis and antibiotic treatment of SAP was as important to participants in our study. Our findings suggest that participants in the UK placed similar importance on radiological findings as in Germany. It is also important to highlight the similar heterogeneity both studies have across their participants. These could be that clinicians in Germany have similar difficulties when approaching SAP diagnosis, or at the time this study was published, SAP diagnosis was not standardized. This heterogeneity however, leads to further questioning of antibiotic practices as a whole in stroke patients. These two studies highlight the heterogeneity of clinician practices and provide a basis for which possible SAP treatment could be standardised in order to reduce variation in SAP treatment. However, there important differences between the two studies. Our study focused on individual clinician practices, and the other study focused on stroke unit practices which could lead to these differences. Another important difference is their study focused on stroke units, while our study focused on individual clinician practices, which could lead to differences between the studies. Another important difference to highlight is the fact that the clinical definition of probable and definite SAP was published in 2015 (37), 3 years after the study in Germany. This time

difference could possibly lead to a change in mindset and approach to SAP and could explain some of the observed differences.

Our findings suggest that there is could be increased agreement for antibiotic initiation as the patient was described across all scenarios among non-consultants compared to consultants with a higher kappa value of 0.49 among non-consultants compared to the 0.39 value among consultants. Possible explanations for this finding could be that consultants throughout their careers and experiences have developed their own criteria compared to non-consultants who include junior doctors, registrars and nurse practitioners. It is possible that more junior clinicians could tend to follow stricter guidelines for antibiotics or other established criteria, while consultants could rely on their years of experience (155, 156). However, this finding needs to be interpreted with caution, as our sample is skewed towards consultants, and therefore could not be representative of the agreement among non-consultants. Further research into the agreement among non-consultants is needed to clarify this issue.

There are several important implications of our findings. Differing clinician approach to antibiotic initiation, along with a lack of validated and standardised diagnostic algorithms could lead to some patients getting inappropriately treated or not treated. This difference in treatment could lead to consequences for the patient and the healthcare system. Overtreatment with antibiotics leads to microbial resistance to antibiotics, excess costs, potential adverse effects (e.g. drug interactions, diarrhoea) and could lead to worse patient outcomes. On the other hand, failure to provide treatment for an alternative diagnosis, such as for example a pulmonary embolism (157), could lead to worse clinical consequences, as well as delays in receiving the appropriate treatment. Likewise, failure to appropriately receive antibiotics could also lead to worse patient outcomes.

Our study has limitations. We were restricted to a small, self-selected sample that responded to our survey. Such a small sample cannot be guaranteed to be representative of UK clinicians. Our survey was curtailed by the SARS-CoV-2 pandemic, which further contributed adversely to the response

rate. Another important limitation is the preponderance of consultants within the sample, who may have less involvement in antibiotic decision-making, particularly out of routine hours. It would be important to expand the responses from more junior and trainee level clinicians. The survey was completed by only 52% of the respondents. Completion rates for online surveys depend largely on the length of the survey and on the complexity of the questions being asked (158). Though this was not highlighted in the piloting, our survey may have been too long and increasingly complex. This means direct comparisons between the four scenarios was difficult to establish.

5.7 Conclusion

Our study has shown that there is heterogeneity among decision-making for antibiotic initiation for suspected SAP among UK clinicians. It provides insight into a number of different criteria used by clinicians for antibiotic initiation in the UK. It also raises important issues regarding possible standardization for SAP diagnosis and treatment in the UK.

5.8 Appendix

Scenario	Description
1	A 73-year-old admitted to the HASU for TACI 4 days ago, with an NIHSS of 16, presents with a temperature of 38.5°, a RR of 26/ minute, unilateral crackles and purulent cough. Investigations included a chest X-ray showing infiltrates in the inferior right lobe, PaO2 measured at 85 mmHg on room air and CRP of 75 mg/L.
2	A 55-year-old patient, who was admitted into the HASU for a LACI 4 days ago with an NIHSS of 11, presents with coughing, a temperature of 38 degrees Celsius and a respiratory rate of 20/minute. The junior doctor on call decided to organize further investigations, which included a chest x-ray with no abnormalities and a CRP measured at 25 mg/L.
3	A 93-year-old patient admitted to the HASU with a POCI 4 days ago and an NIHSS of 5, presents with a temperature of 36.5 degrees Celsius, cough, unilateral crackles and a respiratory rate of 17/ minute. The junior doctor on-call sent a chest x-ray and it showed no abnormalities. Additional tests include a total WBC of 10.7×10^9/L.
4	An 85-year-old patient who was admitted to the HASU due to a TACI 4 days ago with an NIHSS of 21, presents with a temperature of 37 degrees Celsius, a respiratory rate of 20/minute, O2 saturation level of 92% on room air, and dysphagia after a SLT assessment. No other respiratory symptoms are present. The junior doctor on call decided to send a chest x-ray and it shows no abnormalities. Additional tests include a CRP measured at 75 mg/L.

Table 5.8.1. Description for each of the scenarios in our study. HASU – Hyperacute stroke unit, TACI – total anterior circulation infarct, NIHSS – National institute of health stroke scale, PaO2 – Oxygen arterial pressure, CRP – C-reactive protein, LACI – lacunar infarct, POCI – posterior circulation infarct, WBC – white blood cell count, SLT- speech and language therapist

Chapter 6 - Do stroke care processes modify clinical outcomes in stroke associated pneumonia patients after 7 days in hospital? A registry cohort study in England and Wales

6.1 Preface

Throughout the thesis I have shown that SAP variation is accounted minimally by non-modifiable factors, the timing of certain stroke care processes were associated with the development of SAP and there is widespread variation in the thresholds and characteristics used by clinicians in the UK to initiate antibiotics in suspected SAP. However, the question of the burden of SAP on patients remain unanswered. It is important to address this question, because while there is previous evidence demonstrating the association of SAP with worse outcomes, there is still a gap in evidence in the addition of stroke care processes to the question of clinical outcomes in SAP. I attempt to answer this question in the following chapter.

6.1 Preface

6.2 Abstract

6.2.1 Introduction

Stroke associated pneumonia (SAP) is adversely associated with clinical outcomes, but how stroke care modifies these relationships is unclear. We investigated the relationship between SAP and clinical outcomes in England and Wales, adjusting for confounding effects of stroke care processes and their timing.

6.2.2 Methods

The Sentinel Stroke National Audit Programme provided patient data for all confirmed strokes between April 2013 and December 2018. SAP was defined as antibiotic initiation for suspected SAP within the first 7 days from stroke admission. We compared SAP vs non-SAP for the outcomes: length of stay, modified Rankin Scale, and in hospital mortality in appropriate multilevel mixed models. Each model was adjusted for patient and clinical characteristics, as well as markers of stroke care within the first 72hrs. The appropriate effect estimates and corresponding 95% Confidence Intervals were reported.

6.2.3 Results

Of 201778 patients, SAP was present 14.2%. After adjustment for markers of stroke care and clinical characteristics, patients with SAP had an increased risk of longer length of in-hospital stay (IRR of 1.27; 95% CI 1.25, 1.30), increased odds of worse functional outcome at discharge (OR of 2.9; 95% CI 2.9, 3.0) and increased risk of in-hospital mortality (HR of 1.78; 95% C.I. 1.74, 1.82).

6.2.4 Conclusion

We show for the first time that SAP, compared to non-SAP after 7 days of inpatient care, remains associated with poorer clinical outcomes, even after adjusting for markers of stroke care. Research and implementation of preventive measures is needed to reduce the burden of SAP.

6.3 Introduction

Stroke associated pneumonia (SAP) occurs in around 8-13% of people hospitalised with stroke (35, 76), with limited preventive strategies. Previous studies around the world have shown that SAP increases mortality, in-hospital stay and healthcare costs (41, 59, 115). However, whilst the majority of these studies have adjusted for potential confounding effects of baseline patient characteristics on admission (2, 15, 41, 159), the role of acute stroke care such as the timing of thrombolysis or timing of specific assessments has not been considered. Delays in certain care processes have been associated with the development of SAP (160), and therefore analysing the possible influence they might have along with SAP on clinical outcomes merits further research. Another limitation of the existing evidence is that most of the reported outcomes are binary, such as dichotomising the modified Rankin Scale (mRS) into independent and dependent (161), which limits the conclusions that can be drawn from the studies because the dichotomisation of the mRS makes it lose its granularity and limit the findings of worse mRS scores. There is also the potential issue of bias by both extremes in stroke severity, where very mild strokes could lead to earlier discharge and severe stroke could lead to an early death, therefore masking the actual influence of SAP on clinical outcomes and limiting the existing evidence.

Exploring the potential confounding of stroke care processes on outcomes in SAP is important as it could have possible implications for clinical practice and delivery of stroke unit care. The main aim of this study was to investigate the association of SAP with clinical outcomes in patients who stayed in hospital after seven days, whilst exploring the influence of the confounding effects of baseline clinical characteristics and markers of acute stroke care.

6.4 Methods

6.4.1 Data source

The Sentinel Stroke National Audit Programme (SSNAP) is a mandatory registry of stroke patients entering hospital in England, Wales and Northern Ireland. The SSNAP registry was implemented in

2013 by the Intercollegiate Stroke Working Party (53), and was designed to gather baseline characteristics, demographics and stroke care measures. Its main aim is to use these to provide quality improvement data across the entire stroke care pathway, from the pre-hospital phase to six-month follow up. It falls under the purview of the Healthcare Quality Improvement Partnership (HQIP), which in turn controls access to the data. HQIP approved the final data transfer. All data access requests must be made directly to HQIP.

6.4.2 Study design

The SSNAP data here formed an observational cohort of patient level data for all confirmed strokes from April 1st 2013 to December 31st 2018 in England and Wales. A stroke patient was defined as having SAP in our study if they were recorded as having a new antibiotic initiation for suspected pneumonia within the first 7 days of admission. We excluded patients who were discharged or died in the first 7 days in order to remove the differential time component of the definition of antibiotic initiation in the two comparison groups. Patients with greater than 365 days or stroke units with less than 150 admissions per year were also excluded. This was in order to improve the representativeness of the follow up period in the two comparison groups, and the stroke units included in the study i.e. removal of those stroke units that had been repurposed for a small population of stroke patients (142).

6.4.3 Clinical outcomes

The clinical outcomes were mRS on discharge from hospital, total length of in-hospital stay until discharge from hospital; and in-hospital mortality. Both length of stay in hospital and in-hospital mortality were recorded in days.

6.4.4 Clinical characteristics

Patient and clinical characteristics associated with worse clinical outcomes and with SAP in previous studies were identified. These included patient age, sex, National Institute of Health Stroke Scale (NIHSS) stroke severity on admission , pre-morbid mRS on arrival, and the presence of other

comorbidities such as congestive heart failure (CHF), diabetes, atrial fibrillation (AF??), hypertension

and previous stroke or transient ischaemic attack (TIA) (142, 162).

6.4.5 Markers and timing of stroke care

In addition to clinical characteristics, we also adjusted for several markers of stroke care thought to

be associated with both health outcomes and the presence of SAP. These were based on SSNAP's

markers of good quality stroke care (118). The selected markers were arrival at a stroke unit within 4

hours from symptom onset (Yes/No), received a swallow screen within 4 hours from admission

(Yes/No) , assessment by a physiotherapist, speech and language therapist and an occupational

therapist within 72 hours from admission (all in a single composite binary score – Yes – was seen by

all therapists in 72 hours, No – was not seen by all therapists in 72 hours) and if the patient received

thrombolysis (Yes – patient received thrombolysis, No – the patient did not receive thrombolysis).

6.4.6 Statistical analysis and data structure

This SSNAP dataset was representative of the hierarchical structure of stroke care, where stroke

patients were nested within stroke units. To account for the within vs between stroke unit

correlation, a multilevel mixed model approach was selected where stroke unit was set as the

random intercept. Length of in-hospital stay and mRS score on discharge, were modelled using a

multilevel negative binomial model and ordinal logistic model respectively. Time (in days) to in-

hospital mortality post seven days from admission was modelled using a multilevel parametric

survival analysis model using the exponential distribution. This model was chosen over the

proportional hazard function as we believed *a priori* that the proportional hazards assumption would

not hold over the 365 day follow up. A Kaplan-Meier curve described the time to inpatient mortality

between SAP and non-SAP patients after 7 days. Appropriate effect estimates (and 95% Confidence

intervals, CIs) in the form of incidence rate ratio (IRR), odds ratios (OR) and the hazard ratios (HR) are

reported. The clinical outcomes were modelled in three stages to understand the influence of

patient and clinical characteristics, and stroke care markers on clinical outcomes. The first stage

modelled SAP vs non-SAP as a single fixed effect covariate along with the stroke unit random

intercept. In stage two we added the patient and clinical characteristics as fixed effects covariates, and finally in stage three stroke care markers were added to the model.

6.5 Results

The initial dataset obtained from SSNAP comprised of 458, 829 patients across 328 stroke units, of which 39467 (8.6%) were diagnosed with SAP. A total of 5304 (1.2%) patients had missing data regarding SAP status. After applying the exclusion criteria, the dataset comprised of 201,778 patients across 169 stroke units (Figure 1). SAP was present in 28,688 (14.2%) patients, with 2217 (1.1%) patients having missing data regarding SAP status who were consequently excluded. The median length of stay in days for SAP patients was 24 days (IQR 13 – 18), and in non-SAP patients was 18 days (IQR 10 – 35). There was a higher proportion of SAP patients with increased mRS score on discharge compared to non-SAP patients, with 3191 (7.3%) having a mRS of 3, 5992 (12.8%) having an mRS of 4, 5664 (23.4%) having an mRs of 5 and 11425 (32.9%) having an mRS of 6. The median time to in-hospital death for SAP patients was 15 days (IQR 9-26), and the median for non-SAP patients was 15 (IQR 9-28). A full description of clinical characteristics and clinical outcomes can be found in Tables 1 and 2.

We analysed a final sample size of 199,561 patients after accounting for missing data for SAP. In patients with SAP remaining in hospital after 7 days, there was an increased length of stay with an IRR of 1.27 [95% CI 1.25 to 1.30]. In patients surviving to at least 7 days, SAP was associated with an increased disability on discharge, with an OR of 2.9 [95% CI 2.9 to 3.0]. Finally, patients with SAP surviving to at least day 7 after admission had an increased risk of in-patient mortality (HR 1.78 [95% 1.74 to 1.82)]. Results of the analysis of each outcome are presented in Table 3, with a full description of the results available in Tables 1 to 3 of the supplementary material.
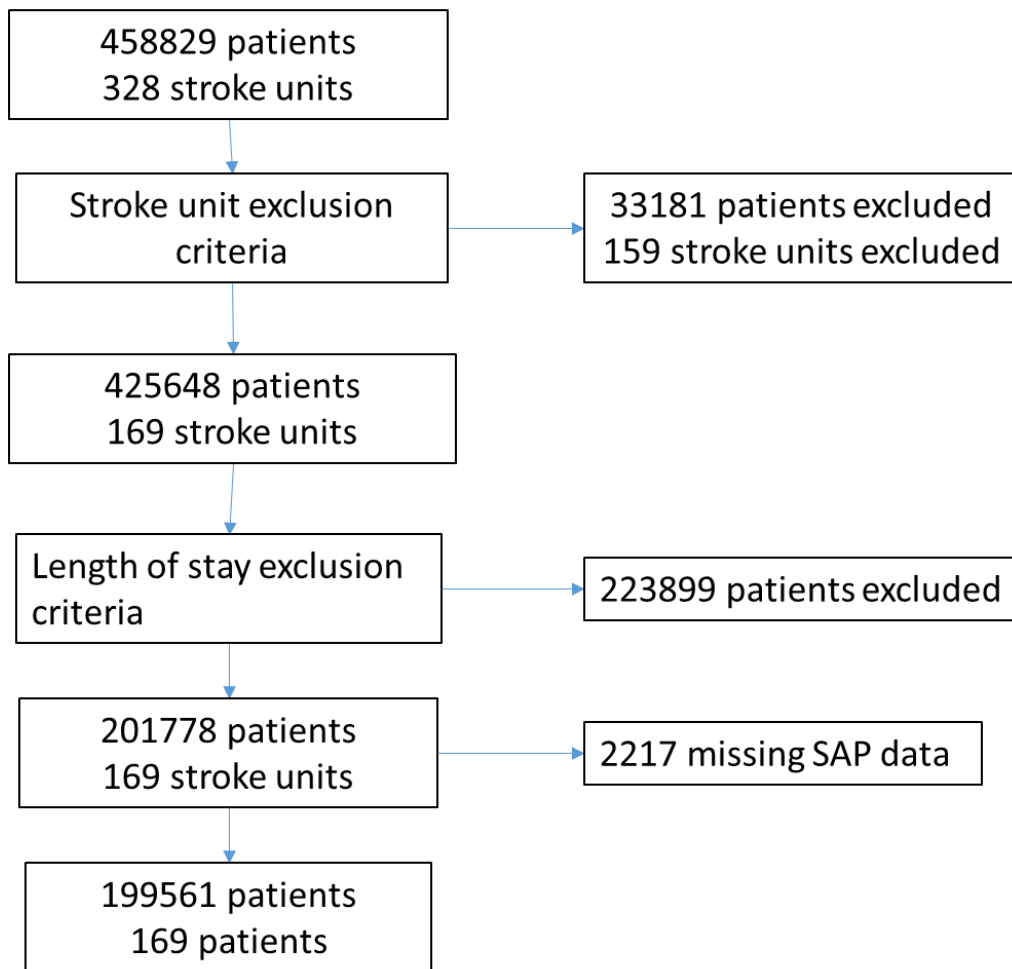
Figure 6.5.1. Flow chart describing how we arrived at the final sample size

CLINICAL CHARACTERISTIC/ STROKE CARE MARKER	SAP (N=28688)	NON-SAP (N=170873)	MISSING (N=2217)
MEDIAN AGE (IQR)	82 (75 – 88)	80 (71 – 86)	81 (71 – 87)
FEMALE	14799 (13.7%)	92244 (85.2%)	1240 (1.1%)
MALE	13889 (14.9%)	78629(84.1%)	977(1.0%)
CONGESTIVE HEART FAILURE	2376 (18.9%)	9989 (79.6%)	178 (1.4%)
ATRIAL FIBRILLATION	8594 (17.9%)	38755 (80.8%)	559 (1.2%)
HYPERTENSION	15812 (14.3%)	93783 (84.7%)	1127 (1.0%)
PREVIOUS STROKE OR TIA	8211 (14.4%)	48283 (84.6%)	570 (0.9%)
DIABETES	5983 (13.8%)	36917 (85.1%)	482 (1.1%)
mRS ON ARRIVAL			
0	10848 (11.8%)	79944 (87.0%)	1013 (1.1%)
1	4490 (13.9%)	27303 (84.9%)	331 (1.0%)
2	3924 (15.5%)	21145 (83.4%)	268 (1.1%)
3	5332 (17.1%)	25533 (81.8%)	332 (1.1%)
4	3171 (18.8%)	13506 (79.9%)	206 (1.2%)
5	923 (20.8%)	3442 (77.6%)	67 (1.5%)
MEDIAN NIHSS ON ARRIVAL	12 (5-19)	6 (2 – 12)	
ARRIVAL TO STROKE UNIT WITHIN 4 HOURS			

FROM SYMPTOM ONSET			
NO	23238 (13.9%)	141447 (84.9%)	1727 (1.03%)
YES	4806 (15.9%)	25173 (83.1%)	331 (1.10%)
UNKNOWN TIME	644 (12.7%)	4253 (84.1%)	159 (3.14%)
THROMBOLYSIS	3802 (16.6%)	18881 (82.4%)	239 (1.04%)
ALL THERAPY SSNAP STANDARD MET			
YES	6629 (8.48%)	70904 (90.7%)	653 (0.83%)
NO	22053 (17.8%)	99955 (80.9%)	1561 (1.3%)
SWALLOW SCREEN SSNAP STANDARDS MET			
YES	20607 (14.6%)	119062 (84.3%)	1552 (1.10%)
NO	8063 (13.3%)	51741 (85.6%)	661 (1.10%)

Table 6.5.1. Summary statistics for the clinical characteristics included in the study – mRS – Modified

Rankin Scale, TIA – Transient Ischaemic attack,

CLINICAL OUTCOME

SAP Status	Median length of stay in days (IQR)	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6 (died in-hospital)	Median time to in-hospital death in days (IQR)
SAP (n=28688)	24 (13 − 48)	351 (4.1%)	746 (4.1%)	1319 (5.1%)	3191 (7.3%)	5992 (12.8%)	5664 (23.4%)	11425 (32.9%)	15 (9 − 26)
Non-SAP (n=170873)	18 (10 − 35)	7935 (93.9%)	17326 (95.1%)	24511 (94.0%)	39820 (91.9%)	40406 (86.3%)	18292 (75.6%)	22583 (65.1%)	15 (9 − 28)
Missing (n=2217)	20 (11 − 41)	158 (1.8%)	153 (0.8%)	222 (0.8%)	340 (0.7%)	410 (0.8%)	226 (0.9%)	708 (2.0%)	14 (9 − 26)

Table 6.5.2. Summary statistics of the clinical outcomes included in the study
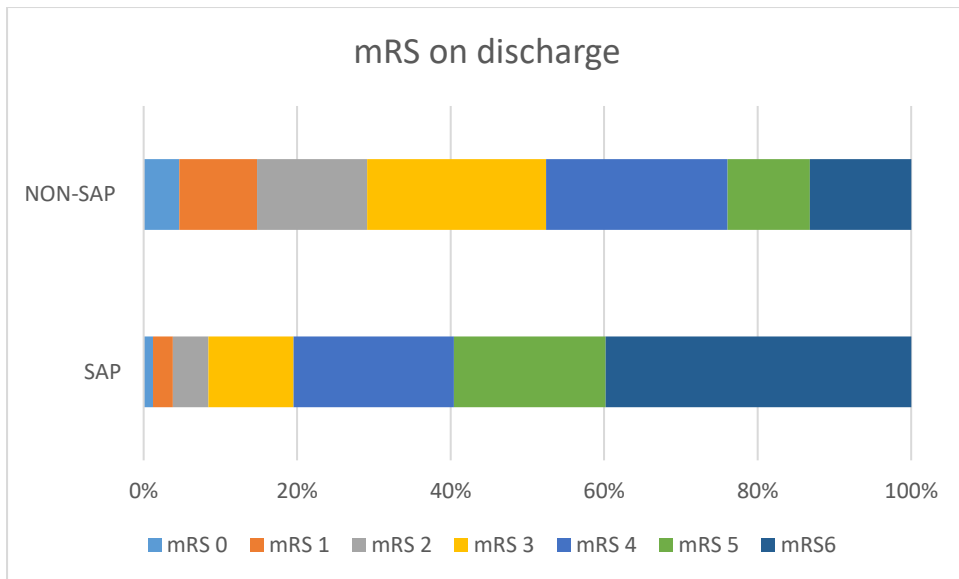
Figure 6.5.2 - Stacked bar charts showing proportion of patients with each mRS score at discharge in SAP patients and non-SAP patients.

CLINICAL OUTCOME	UNADJUSTED	CLINICAL CHARACTERISTICS	STROKE CARE MARKERS AND CLINICAL CHARACTERISTICS
LENGTH OF STAY IN HOSPITAL (IRR)	1.39 (1.37 to 1.41)	1.28 (1.27 to 1.30)	1.27 (1.25 to 1.30)
mRS ON DISCHARGE (OR)	4.5 (4.4 to 4.6)	3.1 (3.0 to 3.2)	2.9 (2.9 to 3.0)
IN-HOSPITAL MORTALITY (HR)	2.4 (2.3 to 2.4)	1.8 (1.7 to 1.9)	1.78 (1.74 to 1.82)

Table 6.5.3. Association between SAP and clinical outcomes. IRR – Incidence rate ratio, OR – odds ratio, HR – Hazard ratio. Clinical characteristics included in models - age, sex, hypertension, congestive heart failure, diabetes, previous stroke, NIHSS score, mRs on admission. Markers of stroke care included in final model - arrival at a stroke unit within 4 hours from symptom onset (Yes/No), received a swallow screen within 4 hours from admission (Yes/No), assessment by a physiotherapist, speech and language therapist and an occupational therapist within 72 hours from admission (single composite binary score Yes/No) and thrombolysis (Yes/No)
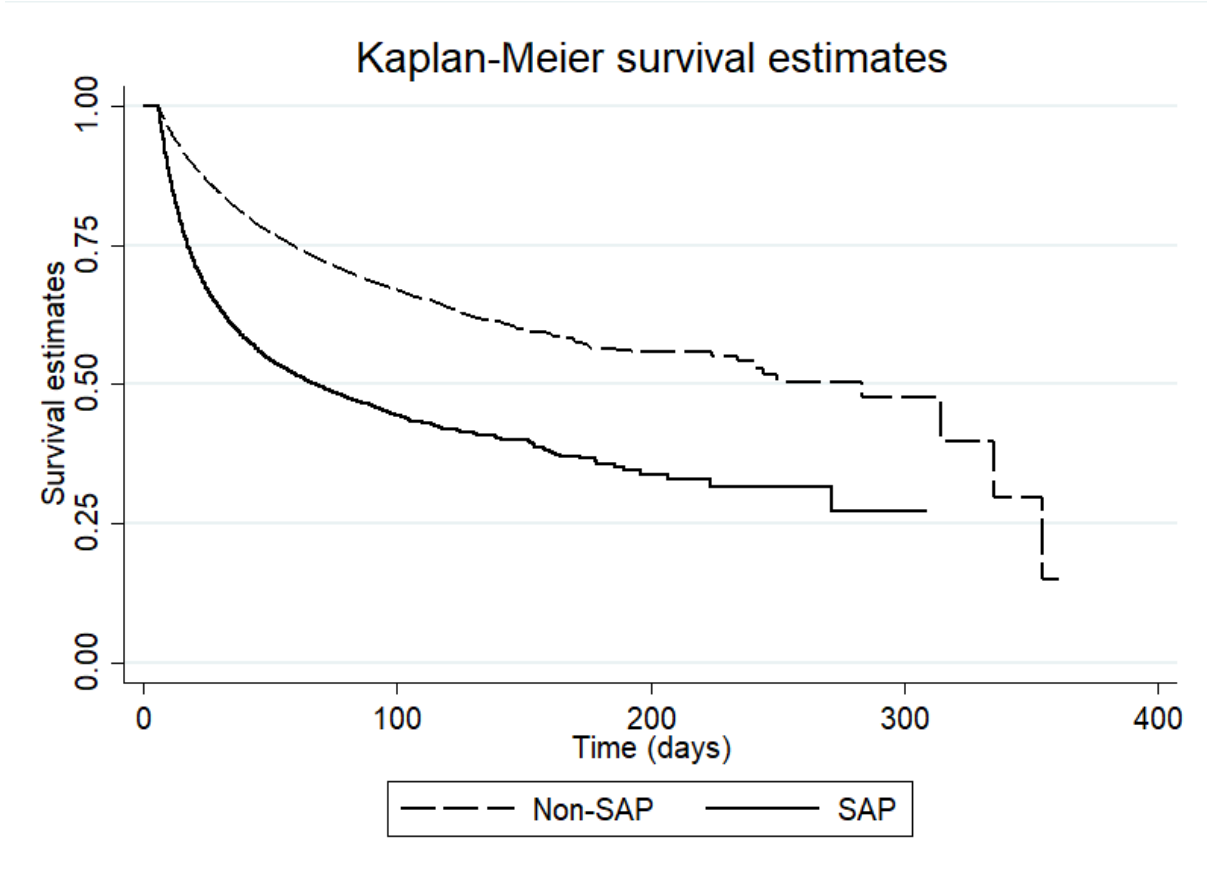
Figure 6.5.3. Kaplan Meier curve showing survival comparisons between SAP and non-SAP patients

6.6 Discussion

Our findings have shown that in a large national registry representative of real-world UK stroke unit care, SAP is associated with worse clinical outcomes in stroke patients despite adjustment for measured patient, clinical and care marker characteristics. Compared to patients with no SAP, patients with SAP surviving to at least 7 days had a 28% increased risk of longer length of stay, three fold increased odds of a worse functional outcome at discharge, and 78% increased risk of in-hospital mortality. While our findings are consistent with existing literature (41, 122, 162), we only included patients who remained in hospital after the initial 7 day exposure period for SAP. By using this approach, we accounted for the potential misclassification bias in SAP diagnosis itself, and between our comparison groups related to the time-dependent nature of SAP diagnosis in our data. This is because milder strokes could have been discharged before seven days, and severe strokes could have died within the first seven days in both cases before SAP was diagnosed. Our approach accounts for this potential influence and is more representative of SAPs association with clinical outcomes. We also show that the addition of markers and timing of stroke care processes only mitigate the impact of these outcomes minimally. SAP remains an independent factor for poor outcomes even after adjusting for the aforementioned markers of stroke care and patient clinical characteristics.

In a previous UK study, SAP was associated with increased mortality (41), but that study focused on a single centre in the East of England. Our study is the first to look at the impact of SAP on a national scale in the UK. While our findings are consistent with existing evidence (161) , they also provide important insight into the relationship between patient care, SAP and clinical outcomes. Secondly, by focusing on this population, our study also removed the influence of uncertain time varying SAP diagnosis on the comparison groups, because there is uncertainty on the timing of SAP diagnosis due to the way SAP is recorded in SSNAP.

SAP was associated with poorer clinical outcomes, which is corroborated by previous evidence (34, 163). The observed association between SAP and poorer clinical outcomes could have several

potential explanations, including by inducing neurological deterioration or impairing neurological recovery. SAP has been shown to exacerbate pro-inflammatory and acute phase responses, which along with hypoxia and other metabolic derangements could exacerbate acute ischaemic injury or impair reparative and recovery pathways (164, 165). SAP is associated with recurrent in-hospital ischaemic stroke, which could also adversely influence subsequent clinical outcomes (163). It is also associated with an increased risk of delirium in the short term and cognitive decline in the longer term (162, 166). Increased medical support during treatment of SAP is likely to influence increased length of stay and temporarily disrupt rehabilitation (108, 109, 167). However, in this possible explanation one would have to be wary of the possibility of reverse causality, as the diagnosis of SAP could cause delays in receiving stroke care and our findings could be reflecting this (41, 162, 168).

There are important aspects to mention when analysing the influence of the timing of stroke care markers and SAP on clinical outcomes. The effect of SAP on clinical outcomes remains independent after adjusting for stroke care markers. A possible explanation for this could be that said care markers are focused on improving clinical outcomes rather than preventing SAP, and we can see this in the reduction of IRR, OR and HR in each of our models. Another possibility is that these markers could be associated with early discharge and have limited impact on those with longer term inpatient health outcomes. Limited granularity of the data on stroke care markers may have contributed to residual confounding and limit our interpretation of their influence. While our findings compound on existing evidence for good quality stoke care and outcomes (169), there are certain aspects of stroke care that need to be analysed further, such as the amount of physiotherapy a patient receives, what clinical care making decisions were made such as positioning or nasogastric feeding, or what type of specific treatment each patient received. Analysing these variables could add further granularity to the existing evidence surrounding stroke care.

Our findings have possible implications for clinical practice. Currently there are no validated guidelines specifically addressing prevention and management of SAP, with the closest available

evidence being a consensus antibiotic approach by the Pneumonia in Stroke Consensus Group (PICSES) (107). Previous evidence has suggested that delays in certain stroke care processes lead to increased risk of development of SAP (170). Targeting these care processes could be an important first step in reducing the burden of SAP on stroke patients. There have also been several clinical trials and observational studies in select populations looking at different preventative measures which can reduce the risk of SAP development. Among these include the use of cilostazol, Angiotensin Converting Enzyme Inhibitors (ACEI) and oral healthcare (94, 97, 104). Investigating these measures in a real world setting to see their possible benefit could provide a starting point in the mitigation of SAP's impact on stroke patients. The other possibility, as mentioned beforehand, would be to develop new ways of treating patients with SAP. Antibiotics remain the mainstay of SAP treatment, and observational data have shown that macrolides might improve outcomes compared to other classes of antibiotics (107, 109) . By implementing these recommendations and interventions the influence of SAP on clinical outcomes could be mitigated. Further research is needed to determine which interventions could be added or modified to reduce the effect SAP has on clinical outcomes.

Our study has several strengths. These include the large sample size of national data with a high-case ascertainment and a more granular dataset make our findings more generalizable. Second, the availability of more detailed measures of health outcomes provides more robust findings, as most of the literature has focused on simpler binary outcome present or not (41, 122) rather health outcomes measured on an ordinal scale or include time to outcome as used here. However, our study also has several limitations. The covariates included in the model were limited by the data recorded in SSNAP, with several unmeasured factors that that have the potential to contribute to residual confounding. Among these include baseline characteristics such as dementia or chronic chest disease, additional detail of treatment received, such as how many sessions with physiotherapy and therapy duration, severity of SAP, microbiological aetiology and antibiotics received. Another layer of confounding we could not account for was organizational level aspects,

such as nursing staff or therapist levels or stroke unit capacity, which could also influence clinical

outcomes. We were also limited regarding the detail of mortality, as we did not have access to the

cause of death or if SAP has an association with death after discharge.

6.7 Conclusion

Our findings indicate that SAP continues to be associated with clinical outcomes in stroke patients

who have stayed in hospital after seven days, even after adjustment for baseline prognostic factors

and acute care processes. Our findings also highlight the need to improve the prevention,

management and treatment of SAP.

6.8 Appendix

CLINICAL CHARACTERISTIC	INCIDENCE RATE RATIO (SINGLE SAP COVARIATE)	95% CONFIDENCE INTERVAL	INCIDENCE RATE RATIO (CLINICAL CHARACTERISTICS)	95% CONFIDENCE INTERVAL	INCIDENCE RATE RATIO (FULL MODEL)	95% CONFIDENCE INTERVAL
SAP	1.39	1.37 to 1.41	1.28	1.27 to 1.3	1.27	1.25 to 1.30
DECADE	-	-	1.0	0.99 to 1.0	1.0	0.99 to 1.0
MALE	-	-	1.02	1.01 to 1.03	1.02	1.02 to 1.04
NIHSS ON ARRIVAL	-	-	1.02	1.02 to 1.03	1.02	1.02 to 1.03
MRS ON ARRIVAL	-	-	0.97	0.97 to 0.98	0.97	0.97 to 0.98
CONGESTIVE HEART FAILURE	-	-	0.97	0.95 to 0.99	0.97	0.95 to 0.99
ATRIAL FIBRILLATION	-	-	0.98	0.97 to 0.99	0.97	0.95 to 0.99
DIABETES	-	-	1.01	1.00 to 1.02	1.01	1.00 to 1.02
PREVIOUS STROKE OR TIA	-	-	0.99	0.98 to 1.00	0.99	0.98 to 1.00
HYPERTENSION	-	-	1.02	1.01 to 1.03	1.02	1.01 to 1.03
ARRIVAL AT A STROKE UNIT WITHIN 4 HOURS FROM SYMPTOM ONSET						
YES	-	-	-	-	1.02	1.01 to 1.04

UNKNOWN TIME OF ARRIVAL	-	-	-	-	0.77	0.74 to 0.79
THROMBOLYSIS	-	-	-	-	0.94	0.92 to 0.96
ALL THERAPY MARKERS MET	-	-	-	-	0.80	0.79 to 0.81
SWALLOW SCREEN SSNAP STANDARD MET	-	-	-	-	0.96	0.95 to 0.97

Table 6.8.1. Multilevel negative binomial regression results displayed as incidence rate ratios, describing the relationship between covariates and length of stay. TIA – transient ischaemic attack

CLINICAL CHARACTERISTIC	ODDS RATIO (SINGLE SAP COVARIATE)	95% CONFIDENCE INTERVAL	ODDS RATIO (CLINICAL CHARACTERISTICS)	95% CONFIDENCE INTERVAL	ODDS RATIO (FULL MODEL)	95% CONFIDENCE INTERVAL
SAP	4.5	4.4 to 4.6	3.1	3.0 to 3.2	2.9	2.9 to 3.0
DECADE	-	-	1.35	1.34 to 1.36	1.35	1.34 to 1.37
MALE	-	-	1.0	0.99 to 1.0	0.99	0.98 to 1.01
NIHSS ON ARRIVAL	-	-	1.1	1.1 to 1.1	1.1	1.1 to 1.1
MRS ON ARRIVAL	-	-	1.44	1.43 to 1.45	1.42	1.41 to 1.43
CONGESTIVE HEART FAILURE	-	-	1.0	1.0 to 1.1	1.0	0.99 to 1.1
ATRIAL FIBRILLATION	-	-	1.1	1.1 to 1.1	1.11	1.08 to 1.13
DIABETES	-	-	1.1	1.0 to 1.1	1.07	1.05 to 1.1
PREVIOUS STROKE OR TIA	-	-	0.94	0.93 to 0.96	0.94	0.92 to 0.95
HYPERTENSION	-	-	0.93	0.91 to 0.95	0.94	0.92 to 0.96

ARRIVAL AT STROKE UNIT WITHIN 4 HOURS FROM SYMPTOM ONSET						
YES	-	-	-	-	1.02	1.0 to 1.05
UNKNOWN TIME OF ARRIVAL	-	-	-	-	1.15	1.09 to 1.2
THROMBOLYSIS					0.69	0.67 to 0.71
ALL THERAPY MARKERS MET	-	-	-	-	0.70	0.69 to 0.71
SWALLOW SCREEN SSNAP STANDARD MET	-	-	-	-	0.95	0.94 to 0.97

Table 6.8.2. Multilevel ordered logistic regression results describing the relationship between fixed effects covariates on modified Rankin scale score on discharge

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CLINICAL CHARACTERISTIC	HAZARD RATIO (SINGLE SAP COVARIATE)	95% CONFIDENCE INTERVAL	HAZARD RATIO (CLINICAL CHARACTERISTICS)	95% CONFIDENCE INTERVAL	HAZARD RATIO (FULL MODEL)	95% CONFIDENCE INTERVAL
SAP	2.4	2.3 to 2.4	1.8	1.7 to 1.9	1.78	1.74 to 1.82
DECADE	-	-	1.5	1.5 to 1.6	1.53	1.51 to 1.55
MALE	-	-	1.10	1.07 to 1.12	1.10	1.08 to 1.13
NIHSS ON ARRIVAL	-	-	1.04	1.04 to 1.05	1.05	1.04 to 1.05
MRS BEFORE STROKE	-	-	1.17	1.16 to 1.18	1.15	1.14 to 1.16
CONGESTIVE HEART FAILURE	-	-	1.2	1.1 to 1.3	1.21	1.16 to 1.25
ATRIAL FIBRILLATION	-	-	1.3	1.2 to 1.3	1.25	1.22 to 1.28
DIABETES	-	-	1.1	1.1 to 1.1	1.09	1.06 to 1.12
PREVIOUS STROKE OR TIA	-	-	0.96	0.93 to 0.98	0.96	0.94 to 0.98
HYPERTENSION	-	-	0.91	0.88 to 0.93	0.91	0.89 to 0.93

ARRIVAL AT STROKE UNIT WITHIN 4 HOURS FROM SYMPTOM ONSET	-	-	-	-	-	-
YES	-	-	-	-	1.01	0.98 to 1.04
UNKNOWN TIME OF ARRIVAL	-	-	-	-	1.96	1.85 to 2.08
THROMBOLYSIS	-	-	-	-	0.79	0.76 to 0.82
ALL THERAPY MARKERS MET	-	-	-	-	0.76	0.73 to 0.80
SWALLOW SCREEN STANDARDS MET	-	-	-	-	1.05	1.04 to 1.05

Table 6.8.3. Multilevel parametric survival analysis results describing the relationship of clinical characteristics with in-hospital mortality. mRs – Modified Rankin Scale TIA – Transient ischaemic attack

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Chapter 7 - Discussion

7.1 Summary of findings

The research presented in this thesis has shown that SAP is a complex issue that needs to be addressed. Firstly, SAP was shown in chapter 3 to have widespread variation across England and Wales, and when adjusting for clinical characteristics, there were minimal changes in the observed variation. This means that clinical characteristics account for a very small percentage of the observed variation. The second objective was to investigate how stroke care processes and their timing are associated with SAP development. This was addressed in chapter 4, where delays in arriving at a stroke unit, delays in time to being assessed by a stroke specialist and delays in time to being assessed by a physiotherapist were associated with the development of SAP. Conversely, receiving thrombolysis within 40 minutes of arrival at a stroke unit were associated with lower odds of SAP. These findings suggest that care processes might be important in the development of SAP. To complement this study, in chapter 5 a cross-sectional survey was undertaken which investigated the different thresholds clinicians in the UK use to initiate antibiotics for suspected SAP. The findings suggest that clinicians in the UK have differing approaches to antibiotic initiation and thresholds for diagnosing SAP when suspected. This could provide insight, to a limited degree, to the observed variation of SAP reported in chapter 3. After understanding the variation of SAP and possible explanations of non-modifiable and modifiable factors that are associated with its development, it is important to understand what relationship SAP has with clinical outcomes. This was addressed in chapter 6, where I described how SAP is associated with an increased risk for increased length of stay, worse functional outcomes and in-hospital mortality. This chapter shows that SAP is an important complication that has serious ramifications and that it needs to be addressed in clinical practice.

7.2 Significance of findings

There are 4 gaps in knowledge that this thesis has tried to address. The first one is to describe the variation of observed SAP across stroke units in England and Wales. While there was no literature investigating variation specifically, variation of overall SAP frequency could be seen between studies

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and registries as mentioned in chapter 1, seen more clearly in Kishore et al's comparison of registries, where the incidence of SAP ranged from 6.7% to 33% across different registries (35, 36). This variation could lead to overtreatment or undertreatment of SAP, leading to worse clinical outcomes. With the findings in the study of chapter 3 suggesting that non-modifiable factors account for 5% of the observed variation leads to important questions regarding what other factors could account for this variation, and whether these may be modifiable.

The second gap in knowledge is what modifiable factors were associated with SAP development. This has been explored previously in a study done by Ingeman et al, where they showed that patients who complete the criteria of good quality stroke care have reduced risk of developing complications (169). While their study provided insight into the association between medical complications and processes of stroke care, it was not trying to answer the question specifically of SAP. I have looked at how timings of stroke care processes were associated with SAP development. This study is novel and brings to light important insight into how delays in the stroke care pathway are associated with to SAP development. It is also important to note that the methodology, using VanderWeele's confounder selection method is novel in the field of stroke associated pneumonia and avoids the table 2 fallacy (133, 141). This provides more robust findings and leads to important questioning of clinical practice.

The third gap in knowledge is to better understand what were the diagnostic approaches used by clinicians to initiate antibiotics in suspected SAP. I tried to address this with an electronic survey involving clinical scenarios of varying ambiguity of suspected SAP based on the PISCES diagnostic criteria. The findings are important because I show that there is variation in the way clinicians approach antibiotic initiation for suspected SAP, and that there's a possibility for antibiotic overuse due to clinician behaviour. A previous study done in Germany by Harms et al also tried to approach this issue and showed similar heterogeneity in their findings when analysing German stroke units

approach of suspected SAP (138). While there are important differences between the 2 studies, they both provide evidence and call for studies with a greater sample size to study clinician behaviour.

The fourth gap in knowledge is to describe the association between SAP and clinical outcomes in the UK in patients who stayed in hospital after 7 days. The study was also novel by adjusting for markers of stroke care. By adjusting for these markers, and by focusing on patients who stayed in hospital after 7 days, the effect of SAP on clinical outcomes is can be seen more clearly without the possible masking of the stroke itself on the same outcomes due to stroke severity. Clinical outcomes of SAP had been studied in the UK before by Teh et al, however, the previous study focused on a single centre regional population, looked at functional outcomes in a binary way, as well as analysing in-hospital mortality with a logistic regression (41). While the findings of the study are comparable to mine, with SAP patients having an increased odds of in-hospital mortality with an OR of 5.87 (95% CI 4.97 to 6.93) compared to non-SAP patients, my findings have important characteristics that improve their generalizability. Firstly, having a larger and more granular dataset improves the strength behind the quantification of SAP mortality in the UK, secondly, my study contains all of the known stroke units that adhere to SSNAP which account to more of the 90% of registered stroke units in the UK, and thirdly, by using a multilevel parametric survival analysis, I account for the time to in-hospital death, which would've been a major confounder in Teh et al's study. My study presented here addressed this with a more granular dataset, adding a more robust layer of evidence to this important issue.

The findings of the thesis have important ramifications on different levels of stroke care. The most important aspect to take from the thesis is antibiotic use in SAP in England and Wales, due to the fact that I have been using antibiotic initiation for suspected SAP as a proxy for SAP in my studies due to the way SSNAP records SAP. I have addressed the possibility of antibiotic overuse across chapters 3 and 4, and tried to explore the different characteristics clinicians across the UK use to initiate antibiotics for suspected SAP in chapter 5. Highlighting this issue is important, as mentioned

beforehand, antibiotic overuse leads to antimicrobial resistance and worse clinical outcomes, and antibiotic underuse due to extremely conservative approaches could lead to poor outcomes as well (112, 171). The findings of the thesis suggest that there are aspects of stroke care that could be associated with antibiotic overuse as found in chapter 4. This leads to important implications for clinical practice, which need to be addressed to prevent SAP and reduce antibiotic overuse. It is also important to highlight that the possible targets for developing prevention strategies could be addressed in clinical practice. With clear markers in delays to arrival at a stroke unit, delays in stroke specialist doctor and physiotherapy assessment associated with SAP development, these processes could be explored in more detail and possible interventions developed. These interventions would be with the intention of preventing SAP or early identification to mitigate worse clinical outcomes, which could have relevance to clinical care.

7.2.1 Implications in clinical practice

There are 2 important implications on clinical practice that this thesis highlights. The first implication is the lack of standardisation in the approach of SAP in the UK. While there are guidelines for the treatment of HAP and CAP (172, 173), the closest that exists are the recommendations from the PISCES group on how to diagnose and treat SAP (37, 107). These recommendations still need to be confirmed through validation in clinical practice. However, they are a starting point on how to reach a consensus on the standardisation of SAP diagnosis and treatment, and would require further research.

The other important implication is the association of certain aspects of stroke care with the development of SAP. While the findings of the thesis focus on timing of stroke care processes, they provide important insight into how clinical practice can be associated with the development of medical complications of stroke. This finding implies that stroke care is a process that needs to be continuously improved upon, in order to prevent the development of complications. It also provides possible insight into specific clinical practices taking place across stroke units, such as thrombolysis

or assessment by specialists in order to either adopt measures to improve these aspects of stroke care, or look at possible reorganization to continue to improve stroke care.

Another implication, mentioned in chapter 2, is the exclusion of smaller stroke units from the analysis in this thesis. While the exclusion was done to have a better representation of stroke care as a whole in England and Wales, it is important to mention that the conclusions gained from said analysis would not necessarily be representative of what happens in smaller stroke units. Some smaller stroke units could have limitations when it comes to stroke care, i.e, different organizational aspects, different care processes, or different staff availability compared to the larger stroke units. It would be a future avenue of research to understand how the smaller stroke units compare to the large, more established stroke units, and if the effects seen in my research are similar of different for SAP patients in these smaller units.

7.3 Strengths and limitations

The strengths and limitations of each study are addressed in each chapter, but are important to highlight again as a whole. Using a dataset with real-world implications brings an additional layer of evidence that was needed in SAP to ascertain the significance it has on a national level in a developed nation. Real world data (RWD) brings additional layer of importance to clinical findings that are not controlled in specific environments, such as RCTs. This means that RWD can be used to inform and complement existing findings to aid in the development of new therapies or interventions in the field of SAP, as they are more representative of what happens to the patient in a non-controlled environment (174, 175). Its size and high-case ascertainment make the findings of this thesis more generalizable for stroke care across the UK and possibly overseas, as stroke care processes not specific to the UK, such as time to arrival at a stroke unit or time to thrombolysis could be easily transposed into other countries' stroke care practices.

Another important strength in this thesis, is the analysis of stroke care process data. Most of the literature available that analyses SAP prevalence is focused on non-modifiable factors, such as

clinical characteristics. With the inclusion of stroke care process data provides important insight into modifiable factors that could be addressed to prevent SAP.

However, there are important limitations that need to be acknowledged. Firstly, I was limited to the variables that SSNAP records. Among these include factors that could be causing important confounding in my findings that are known risk factors for SAP. These factors include smoking status, the presence of any pulmonary disease and the presence of any oncological or immunological conditions (45, 56, 59). Another important limitation that we could not account for was the organizational aspects of the stroke units, such as staffing levels, geography, stroke unit size, etc. While I attempted to mitigate this by selecting stroke units with at least 150 stroke admissions per year, I could not account for these additional unit-level factors. As I mentioned beforehand, the assumption was made that stroke units with a higher intake would have more established organisations in terms of stroke care, and by excluding the smaller stroke units, I accounted, though to a limited and assumed extent, this possible confounding. Although SSNAP does record some of this information, I could not access this level of information due to anonymization concerns. This is key, and compounded with the findings of chapter 3, with clinical characteristics accounting for only 5% of observed SAP variation. There are also important characteristics of in-hospital care that cannot be measured and could also play an important role in SAP development and variation. These could include the level of vigilance clinicians have when approaching SAP, any differences in pneumonia diagnostic and treatment protocols between hospitals, the hospital environment and prevalence of nosocomial bacteria. These unmeasured aspects of stroke care could have some influence in my results and would require further research to determine the impact they could have on both SAP development and clinical outcomes.

Another issue that needs to be addressed is the lack of further granularity of data regarding SAP. Important information such as the type of antibiotic used or the microorganism that was cultured with SAP would've added important granularity to my findings. By not having these data, the

implications of my findings on clinical practice are limited, because antibiotics are determined by the

microorganism and its sensitivity, or likely microorganism in the absence of positive cultures. With

the aim to ultimately improve antibiotic stewardship, having these data would've added an

additional layer of robustness to my findings. Another aspect of further detail that could not be

accounted for was the clinician who started the antibiotics. Whilst I have accounted for the patients

nested within stroke units, I could not account for the individual clinician nesting, which would be of

interest as I have demonstrated with the survey, there is variation at the individual level for

antibiotic initiation with the survey. It is possible that the variation for antibiotic initiation could even

be translated into variation of antibiotic class and diagnostic measures clinicians could use for SAP

diagnosis.

When discussing the limitations of the thesis, highlighting the definition of SAP I used is important

because there is potential for selection bias. I have mentioned this in previous chapters, with the

uncertainty surrounding the definition of SAP, I do not know the diagnostic criteria the clinicians

used to initiate antibiotics in SSNAP. This means that I do not know what the clinicians use to initiate

antibiotics, which to some I extent, I tried to investigate in chapter 5. Not knowing what the criteria

clinicians used to diagnose SAP and initiate antibiotics, as well as which day of the 7 were antibiotics

started leads to potential selection bias by the clinicians and could limit the results of the data

analysis. If I were to design a similar study, I would add more information to the diagnosis of SAP and

not just depend on antibiotic initiation within the first 7 days from stroke admission. I would use the

PICSES criteria of probable and definite SAP, one category for each, which day of the first 7 days was

it diagnosed and what type of antibiotic was used to account for all potential limitations of the

definition of SAP.

Another factor which could limit our findings was the amendment of the dataset between 2020 and

2021. The initial dataset did not include time to in-hospital death and the individual components of

the NIHSS score. When renewing the yearly permission of data use with HQIP, we decided with

SSNAP, to add this information as it was important to analyse the clinical outcomes. When the new dataset arrived, the total number of patients went from 456,590 in 322 stroke units to 458,829 in 328 stroke units. This change in number, while small, still could have influenced the results and limit the conclusions.

7.4 Proposed future work

In this thesis, the importance of SAP as a clinical complication is highlighted. I also show that there are possible targets for intervention in the stroke care pathway, where the odds of developing SAP are increased with delays in specific stroke care processes, such as assessment by a physiotherapist and arrival at a stroke unit. In the literature review I address possible prevention strategies that may be useful in selected populations, such as oral hygiene (103, 105, 176) and the use of metoclopramide (98). These studies were RCTs which show, up to a certain extent, that they could be beneficial in reducing the odds of SAP, and have yet to be adopted into active clinical practice. Using the evidence gathered in the three studies, as well as these measures previously studied, this thesis provides the foundation for a possible ward-based bundle of care to prevent SAP and marshal antibiotic use.

A prospective bundle of care study could either be a randomised or interrupted time series design. This procedure could be the implementation of SAP prediction using the ISAN prediction score in at risk patients. Patients with a high likelihood of SAP would then be flagged for the attending clinician, and start preventive measures. With the available evidence, this could be alerting the physiotherapist to a high risk SAP patient, to the implementation of an oral hygiene solution, to the use of metoclopramide. This proposed intervention would require high coordination between stroke teams, and could also mitigate the worse clinical outcomes found in chapter 6.

However, tackling SAP in the current research environment will be difficult. Currently there are a very limited number of research teams worldwide that are dedicated in researching SAP, and this limits the possibilities of widespread changes to clinical practice and implementation of new

prevention measures. The variability of the definition of SAP in a clinical environment makes it difficult to develop clear inclusion/exclusion criteria for a RCT or a prospective study. Communicating the importance of SAP to other stroke clinicians and researchers is necessary in order to start the process of improving prevention and the development of new treatments. Coordinated efforts by the dedicated SAP research teams will be paramount in the journey of SAP research and the improvement of patients' lives.

7.5 Conclusion

I have shown in this thesis how SAP is a complex issue that needs to be tackled across several fronts. While there are limitations in each of the studies conducted, they provide important insight across the spectrum of the development of SAP, how clinicians approach it and how it worsens clinical outcomes in the UK. This body of work should provide a platform for future work to be conducted to reduce the burden of SAP in patients in the UK, and lead to changes in clinical practice that could improve the lives of patients.

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Appendix

SSNAP Domains and Key Indicators

1. SCANNING

1.1 Proportion of patients scanned within 1 hour of clock start

1.2 Proportion of patients scanned within 12 hours of clock start

1.3 Median time between clock start and scan (hours:mins)

2. STROKE UNIT

2.1 Proportion of patients directly admitted to a stroke unit within 4 hours of clock start

2.2 Median time between clock start and arrival on stroke unit (hours:mins)

2.3 Proportion of patients who spend 90% of their time on a stroke unit

3 THROMBOLYSIS

3.1 Proportion of all patients given thrombolysis (all stroke types)

3.2 Proportion of all eligible patients (according to the RCP guideline minimum threshold) given thrombolysis

3.3 Proportion of patients who were thrombolysed within 1 hour of clock start

3.4 Proportion of applicable patients directly admitted into the stroke unit within 4 hours of clock start AND who either received thrombolysis or have a pre-specified justification for why it was not given

3.5 Median time between clock start and thrombolysis

4 SPECIALIST ASSESSMENT

4.1 Proportion of patients assessed by a stroke specialist consultant physician within 24 hours of clock start

4.2 Median time between clock start and being assessed by stroke consultant (hours:mins)

4.3 Proportion of patients who were assessed by a nurse in stroke management within 24 hours of clock start

4.4 Median time between clock start and being assessed by a stroke nurse

4.5 Proportion of applicable patients who were given a swallow screen within 4 hours of clock start

4.6 Proportion of applicable patients who were given a formal swallow assessment within 72 hours of clock start

5 OCCUPATIONAL THERAPY

5.1 Proportion of patients reported as requiring occupational therapy

5.2 Median number of minutes per day on which occupational therapy is received

5.3 Median % of days as an inpatient on which occupational therapy is received

5.4 Compliance against the therapy target of an average of 25.7 minutes of occupational therapy across all patients

6 PHYSIOTHERAPY

6.1 Proportion of patients reported as requiring physiotherapy

6.2 Median number of minutes per day which physiotherapy is received

6.3 Median % of days as an inpatient on which physiotherapy is received

6.4 Compliance against the therapy target of an average of 27.1 minutes of physiotherapy across all patients

7 SPEECH AND LANGUAGE THERAPY

7.1 Proportion of patients reported as requiring speech and language therapy

7.2 Median number of minutes per day on which speech and language therapy is received

7.3 Median % of days as an inpatient on which speech and language therapy is received

7.4 Compliance against the therapy target of an average of 16.1 minutes of speech and language therapy across all patients

8 MDT WORKING

8.1 Proportion of applicable patients who were assessed by an occupational therapist within 72 hours of clock start

8.2 Median time between clock start and being assessed by an occupational therapist (hours:mins)

8.3 Proportion of applicable patients who were assessed by a physiotherapist within 72 hours of clock start

8.4 Median time between clock start and being assessed by a physiotherapist (hours:mins)
8.5 Proportion of applicable patients who were assessed by a speech and language therapist within 72 hours of clock start
8.6 Median time between clock start and being assessed by a speech and languate therapist (hours:mins)
8.7 Proportion of applicable patients who have rehabilitation goals agreed within 5 days of clock start
8.8 Proportion of applicable patients who are assessed by a nurse within 24 hours and at least one therapist within 24 hours and all relevant therapies within 72 hours

9 STANDARDS BY DISCHARGE
9.1 Proportion of applicable patients screened for nutrition and seen by a dietitian by discharge
9.2 Proportion of applicable patients who have a continence plan drawn within 3 weeks of clock start
9.3 Proportion of applicable patients who have mood and cognition screening by discharge

10 DISCHARGE PROCESS
10.1 Proportion of applicable patients receiving a joint health and social care plan on discharge
10.2 Proportion of patients treated by a stroke skilled Early Support Discharge team
10.3 Proportion of applicable patients in atrial fibrillation on discharge who are discharged on anticoagulants or with a plan to start anticoagulation
10.4 Proportion of those patients who are discharged alive who are given a named person to contact after discharge

Table 8.1.1. Key indicators for high quality care defined by the ICSWP, used by SSNAP. Taken from the SSNAP webpage

Data Access Request Form (DARF)

Applicants should ensure that they have reviewed the accompanying HQIP guidance and have discussed this request with the organisation(s) commissioned by HQIP to deliver the relevant clinical audit or clinical outcome review programme. The audit or clinical outcome review programme acts as data processor to HQIP and is referred to as the 'data provider' for the purpose of this data access request.

Once completed please return this signed form to datasharing@hqip.org.uk

All sections within this form are mandatory unless specifically stated otherwise. Unless this form is completed in full, it will be returned to the applicant which will extend the time to data receipt.

For HQIP office use only			
HQIP application number	DARF296 Amendment and Renewal	**Date of submission to HQIP**	14/07/2020
If applicable, any linked application number(s)	DARF296	**Charging category**	Change
Tracking history	14/07/2020 – Application received. 29/07/2020 – Pre-DARG review completed. The following needs to be addressed: Section 2 – the application should be both for an amendment and a renewal of the existing HQIP296 (due to expire in August 2020) – please tick both categories. Section 3 – you have ticked 'Other', please clarify why the project would not be considered a 'research' one. Section 11 – the data flow refers to SSNAP data as being anonymised, however the request is for de-personalised data (which is usually pseudonymised). Please correct if applicable. 29/07/2020 – Applicant informed of clarifications request.		
Expiry date	Click or tap to enter a date.		

Section 1	Primary applicant information
Title of project	Variation of Stroke Associated Pneumonia across UK stroke units
Name of primary applicant organisation	University of Manchester
Name of any partner organisation (s) if applicable *(ensure partner form also completed)*	Click or tap here to enter text.
Address of primary applicant organisation	Oxford Road, Manchester, M13 9PL

Primary contact *(must be a permanent senior member of staff)*	Craig Smith	Job title	Professor of Stroke Medicine
Telephone	Click or tap here to enter text.	Email	Click or tap here to enter text.

Organisation type	NHS Healthcare Provider	Academic Institution	Healthcare Regulator	Other Healthcare Body
	☐	☒	☐	☐
	Local Authority	**Individual Citizen(s)**	**Commercial Body**	**Other (please state)**
	☐	☐	☐	☐

HQIP projects from which data is requested *(For reference a list of HQIP projects and their Project Managers are listed on the HQIP website)*	**Please list below the name(s) of each of the HQIP-commissioned projects from which you are requesting data.**
	Sentinel Stroke National Audit Programme

Section 2	Application type

Please tick at least one box below confirming whether the application is for a new application, extension or amendment. For extensions or amendments, you must highlight the specific information within this form that has been updated and provide updated signatures in order for the request to be processed.

Request	Provide original HQIP application number and approval date and any subsequent amendment approval dates.	Summary of changes and rationale for the change to your original application. In addition all changes must be made as highlighted edits within this form.
☐ **New Application** Including applications that have not previously been approved by HQIP.	**N/A**	**N/A**
☒ **Extension** Request to extend the term of a current data sharing agreement.	DARF 296, approval date 22/8/2019	See amendment section
☒ **Amendment** Request to change the scope, data fields requested or any other change to an application previously approved by DARG.	DARF 296, approval date 22/8/2019	Addition of time to in-hospital death, and addition of granularity to the NIHSS score on arrival

Section 3	Project type			
Please select the most appropriate answer	**Research**	**Service Evaluation**	**Clinical Audit**	**Other (please state)**
	☐	☐	☐	☒ Quality improvement

Is ethics approval required?	If the request is for research purposes you must enclose evidence of NHS ethics approval or evidence that this is not required	
	YES Confirmation of NHS ethics needs to be submitted with this application.	☐
	NOT REQUIRED Confirmation needs to be submitted with this application from the HRA decision tool **http://www.hra-decisiontools.org.uk/ethics/** or confirmation from your local Research and Development Department that NHS ethics is not required.	☒

Section 4	Project details
Please provide full details of the project below. You should describe and justify the project's objectives, rationale and methodology.	

Objective/Rationale	Pneumonia frequently complicates stroke and has a profound impact on clinical outcomes. As strategies to prevent and treat it are limited, stroke-associated pneumonia (SAP) remains a major area of unmet need in clinical practice and research. In preliminary analyses of SSNAP data, we found that the incidence of SAP is highly variable between stroke units and that this was not explained by differences in casemix, an observation that has considerable implications for antibiotic stewardship and clinical outcomes. Several clinical characteristics such as advancing age, stroke severity and pre-stroke disability all independently predict SAP and stroke unit care processes may influence occurrence of SAP. There is however a lack of standardised approaches to diagnosis and management of SAP and it is not known whether this variation in practice contributes to poorer outcomes in patients with acute stroke.
Methodology	**Please include:** ▪ **A summary of your project methodology, ensuring this description aligns with the dataset requested** ▪ **A justification of sample size, analyses proposed and plans for patient and/or user group involvement**
	Our overall aim is to investigate the variation of SAP prevalence between stroke units and evaluate how patient, unit-level and external factors contribute to this variation. To achieve this aim we will use patient and unit-level data from SSNAP to describe variation in the diagnosis of SAP across all hospitals in England and Wales to address the following objectives: 1. Describe the variation in observed prevalence of SAP recorded between stroke units 2. Describe the patient characteristics (including demographic characteristics, clinical characteristics and socioeconomic deprivation) and (SSNAP reported mortality, length of stay), stratified by the occurrence of SAP 3. Compare the observed prevalence of SAP with the predicted prevalence of SAP based on baseline patient characteristics 4. Determine the temporal trends (over years and across seasons) in the observed and predicted SAP prevalence across stroke units 5. Describe the organisational characteristics of stroke units and care processes in relation to the observed SAP prevalence
Please describe the expected measurable benefits to health and/or social care including target date	We expect to develop a ward tool to reduce the variation of stroke-associated pneumonia in England and Wales to reduce antibiotic overuse and improve clinical outcomes in patients. We hope to develop it by the end of 2021
Proposed completion date of the project	30/06/2022
Lay Title and Summary	**Please provide a lay summary of your project (max 300 words).** The lay summary should be written in plain English and must enable a non- medical audience to understand the research question and aims of the project. If your request is approved, this paragraph (title and summary) will be published on the HQIP website.

Patients with stroke can develop several complications after their admission, among them a complication known as stroke-associated pneumonia (SAP). This complication has been related to increased death and a poorer quality of life in stroke survivors. Previous studies have reported very different levels of patients with SAP, but the reasons for this variation in the levels is still unclear. This variation could lead to misuse of antibiotics in the stroke patient population, which, if left unchecked, could lead to a higher rate of death and poorer quality of life in stroke patients. The main aim of our study is to investigate this variation between care centres in England and Wales, and to provide a basis for better use of antibiotics in stroke patients. Our study will look at different characteristics related to stroke care and patients to see if these features can explain this variation. We hope that by exploring the different possibilities that can cause this variation, we can provide a basis for a tool to marshal antibiotic use in stroke patients, and therefore, provide a better quality care and better quality of life.

Section 5	Publications and other outputs			
Please include all intended outputs of the project including publications. Outputs include all types of disseminations produced from the project data. For each output include the highest level of detail of data/information that will be displayed.				
Outputs including publications *(add more rows if required)*	**What is the highest level of detail that will be displayed in the output** *(e.g. case record, unit, hospital, trust, network, regional, national, whole study, study group)*	**Will this output be published?**	**Expected Date of Publication**	**Confirm that published output will be anonymised to the level required by ISB1523: Anonymisation Standard for Publishing Health and Social Care Data**
Marco Antonio Lobo's PhD Thesis	Anonymous stroke unit	Yes	31/12/2021	Yes
Variation of SAP in England and Wales: a cohort study	Anonymous stroke unit	Yes	31/08/2020	Yes
Impact of stroke care in SAP variation in England and Wales	Anonymous stroke unit	Yes	30/11/2020	Yes
Variation of SAP in England and Wales and its impact in clinical outcomes	Anonymous stroke unit	Yes	01/04/2021	Yes
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.
Add more rows if needed				

Section 6	Project funding

Please indicate whether your project has received dedicated funding. Please also indicate whether there is a commercial interest in the project, either by funding or direct input into project design or team.		

Funding *(please select one answer)*	**No** ☒	
	Yes ☐	**If yes**, please provide the name of the funding body below Click or tap here to enter text.
Commercial interest *(please select one answer)*	**No** ☒	
	Yes ☐	**If yes**, please provide the name of the organisation and the nature of any interest into the project design below. Please also note information required in Section 7 Click or tap here to enter text.

Section 7	Declaration of Interest

Please indicate whether any individuals named in this application have an interest to declare about this application. All interests that might unduly influence an individual's judgement and objectivity in the use of the data being requested from DARG are of relevance. Particular consideration should be given to declaring interests involving payment or financial inducement for use of the data being requested. These will be considered by DARG to determine if there is any potential conflict of interest identified as part of the request.		

Declaration of interest *(please select one answer)*	**No** ☒	
	Yes ☐	**If yes**, please provide the name and details of the declaration for each individual below Click or tap here to enter text.

Section 8	Data Summary

Please tick the box(es) confirming the geographical coverage of the data you are requesting. Coverage is defined as the location of the healthcare services who originated / initially provided the extract of data you are requesting. *NB. HQIP's DARG can only approve applications for access to the datasets which HQIP commission and thereby act as Data Controller.*			

Geographical coverage	☒ **England**	☒ **Wales**	☐ **Scotland**
	☐ **Northern Ireland**	☐ **Republic of Ireland**	☐ **Other**, please state: Click or tap here to enter text.

Inclusion and exclusion criteria (including date parameters)	**Describe precisely the criteria which define the patients to be included and to be excluded from the data extract you are requesting.** Please include precise date parameters for the start and end of the range requested (dd/mm/yy) and explain which dated project field will be used to define the requested cohort (e.g. date of admission or date of operation).
	All cases of confirmed strokes from the 1st of April 2013 to the 31st of December 2018 that have been entered into SSNAP/ cut-off 31st of December 2018

Periodic updates	**Periodic updates may sometimes be available.** These must be agreed with the HQIP data provider in advance and any falling outside of the term of the Data Sharing Agreement will be subject to an application extension being agreed. Please provide details below including reasons.
	☒ **None** ☐ **Monthly** ☐ **Quarterly** ☐ **Bi-annual (6 monthly)** ☐ **Annual** ☐ **Other**, please state: Click or tap here to enter text.

Project/linked data *(please tick all that apply)*	**HQIP commissioned projects routinely link the data that they collect to other external datasets. The requirements of each data controller vary and there may not be an agreed process for onward sharing of linked project data. Please contact HQIP for advice before completing this form if you wish to apply for project data that has been linked with other datasets.** Please confirm whether you are applying for unlinked project data, or project data that has been linked to an external dataset.	
	☒ **Unlinked project data**	☐ **Project data linked with HES**
	☐ **Project data linked with ONS**	☐ **Project data linked with PEDW**
	☐ **Project data linked with Civil Registration data**	☐ **Project data linked with another dataset** Please provide details below: Click or tap here to enter text.

Section 9	Data Type

First discuss your request with the data provider and then indicate in this section the type of data you are requesting (tick all that apply). Note that what is relevant here is the identifiability of the data you are requesting at the point it leaves the HQIP data provider and not the level disclosed in any future publication. For further information on these categories of identifiability please see the Understanding patient data guidance **https://understandingpatientdata.org.uk/what-does-anonymised-mean**	
☐ **Anonymous data** This is information from many people combined together (aggregated), so that it would not be possible to identify an individual from the data. Information about small groups or people with rare conditions could potentially allow someone to be identified and so would not be considered anonymous. Individual patient level data may also very occasionally be categorised as anonymous. In this case, the information in each record requested would also potentially be true for many other similar individuals, and so could not be used to deduce the person's identity.	Click or tap here to enter text.
☒ **De-personalised data** This is information that does not identify an individual, because identifiers have been removed or encrypted. However the information is still about an individual person and so needs to be handled with care. It might, in theory, be possible to re-identify the individual if the data was not adequately protected, for example if it was combined with different sources of information.	**HQIP data provider to provide a description for how the data will be de-identified to reduce any risk of re-identification.**
	Click or tap here to enter text.
☐ **Personally identifiable data** This is information that identifies a specific person. Identifiers might include: name, address, full postcode, date of birth or NHS number. Personally identifiable data fields that are requested solely for the purpose of linkage still need to be described here and in Section 10, even if they are removed before the data reaches the applicant.	Click or tap here to enter text.

Section 10	Data Fields

Please detail in the table below the data fields required as part of this request. All fields required to leave the data provider must be included here including linkage fields. Justification for these should include whether they will be retained or destroyed once linkage is complete. This should also be clear on the data flow map in Section 11. Applicants should only request the minimum data set required to address the purpose stated within this application.

Data field requested	Data source (Audit/project, HES, ONS, PEDW etc.)	Transformation applied This must be completed for every data field requested: • None • Explain the transformation applied (e.g. pseudonymisation (including who holds the key to reverse), time elapsed, age banding etc.)	Justification Please justify your use of each data item requested
EXAMPLE – NHS Number	*EXAMPLE - Audit*	*EXAMPLE – Pseudonymisation and encryption with key held only by HQIP data provider*	*EXAMPLE - For tracking single patients within multiple audit entries*
Admitting team code	Audit	Pseudonymisation and encryption with key only held by SSNAP	Necessary to identify stroke units
Index of multiple deprivation	Audit	None	Necessary for baseline characteristics
1.6 Gender	Audit	None	Necessary for baseline characteristics
1.8 Ethnicity	Audit	None	Necessary for baseline characteristics
1.10 Was the patient already inpatient	Audit	None	Necessary for baseline characteristics
1.14 First ward admitted to first hospital	Audit	None	Necessary for care process evaluation
2.1 Comorbidities prior to admission	Audit	None	Necessary for care process evaluation
2.1.1 Congestive heart failure	Audit	None	Necessary for baseline characteristics
2.1.2 Hypertension	Audit	None	Necessary for baseline characteristics
2.1.3 Atrial Fibrillation	Audit	None	Necessary for baseline characteristics
2.1.4 Diabetes	Audit	None	Necessary for baseline characteristics
2.1.5 Stroke/TIA	Audit	None	Necessary for baseline characteristics

2.2 Modified Rankin Scale before stroke	Audit	None	Necessary for baseline characteristics
2.3 NIHSS score on arrival	Audit	None	Necessary for baseline characteristics
2.3.1 Level of consciousness, if NIHSS not complete	Audit	None	Necessary for baseline characteristics
2.5 What type of stroke it was, infarction or PICH	Audit	None	Necessary for baseline characteristics
2.6 Was the patient given thrombolysis	Audit	None	Necessary for care process evaluation
2.9 What was the patient's NIHSS score after thrombolysis (and thrombectomy)	Audit	None	Necessary for care process evaluation
3.1 Decision for palliative care after 72 hours	Audit	None	Necessary for care process evaluation
4.2 First ward admitted in the hospital	Audit	None	Necessary for care process evaluation
5.1 Worst level of consciousness first 7 days	Audit	None	Necessary for clinical characteristics
5.3 Antibiotics for a newly acquired pneumonia within first 7 days	Audit	None	Necessary for SAP diagnosis
6.6 Screened for malnutrition	Audit	None	Necessary for care process evaluation
7.1 Patient destination	Audit	None	Necessary for endpoints
7.4 Modified Rankin Score at discharge (from final team i.e discharge home or institution)	Audit	None	Necessary for endpoints

7.5 If discharged to care home, previously or not previously a resident	Audit	None	Necessary for endpoints
SSNAP DERIVED VARIABLES			
Age on arrival	Audit	None	Necessary for baseline characteristics
Admission quarter	Audit	None	Necessary for baseline characteristics
Time from symptom onset to arrival at first hospital	Audit	None	Necessary for care process evaluation
Time from onset to arrival at stroke unit	Audit	None	Necessary for care process evaluation
Thrombectomy – time from symptom onset to completion	Audit	None	Necessary for care process evaluation
Arrival in hours or not	Audit	None	Necessary for care process evaluation
Time from clock start to stroke nurse assessment	Audit	None	Necessary for care process evaluation
Time from clock start to OT assessment	Audit	None	Necessary for care process evaluation
Time from clock start to physio assessment	Audit	None	Necessary for care process evaluation
Time from clock start to bedside swallow screen	Audit	None	Necessary for care process evaluation
Time from clock start to specialist speech and language therapist swallow assessment	Audit	None	Necessary for care process evaluation

Dysphagic (Y/N) *dysphagic defined as having had a SALT swallow <u>or</u> were recorded as too medically unwell; not dysphagic defined as SALT swallow assessment not undertake i.e passed bedside swallow test	Audit	None	Necessary for baseline characteristics
Total length of stay for stroke admission	Audit	None	Necessary for endpoints
AMENDMENT VARIABLES			
Time to in-hospital death	Audit	None	Necessary for endpoints
Individual NIHSS components			
Level of consciousness responsiveness	Audit	None	Necessary for baseline characteristics
Level of consciousness questions	Audit	None	Necessary for baseline characteristics
Level of consciousness commands	Audit	None	Necessary for baseline characteristics
Horizontal eye movement	Audit	None	Necessary for baseline characteristics
Visual field test	Audit	None	Necessary for baseline characteristics
Facial palsy	Audit	None	Necessary for baseline characteristics
Motor arm	Audit	None	Necessary for baseline characteristics
Motor leg	Audit	None	Necessary for baseline characteristics
Limb ataxia	Audit	None	Necessary for baseline characteristics

Sensory	Audit	None	Necessary for baseline characteristics
Language	Audit	None	Necessary for baseline characteristics
Speech	Audit	None	Necessary for baseline characteristics
Extinction and inattention	Audit	None	Necessary for baseline characteristics
Day of the week for stroke admission	Audit	None	Necessary for baseline characteristics

Section 11	Processing locations and data flows

Please list all locations where processing will be undertaken, for the avoidance of doubt storage is considered processing. For each separate organisation processing data which is not fully anonymous a separate partner organisation form must also be completed.

Processing location	Organisation name	Processing or storage	Data type processed *(anonymous, de-personalised, personally identifiable)*	How will data be transferred to this location?
Manchester	University of Manchester	Processing	De-personalised	Electronically
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Choose an item.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Choose an item.	Click or tap here to enter text.

Will data be transferred outside of the European Economic Area? *If yes please state to where and give details of how that will be in compliance with the Data Protection Act 2018.*	☒ **No**		☐ **Yes**
	If yes, please provide details: Click or tap here to enter text.		

Data Flows

Please insert a data flow diagram which graphically describes:

1. **All locations where data is processed**
2. **All transfers that take place between locations and organisations**
3. **Data linkages to other data sets**

Please insert data flow diagram here

SSNAP
- Depersonalized data
- Electronic format
- Legal basis-> for research and academic purposes
- Linked data within SSNAP (anonymized data)

↓

The University of Manchester
- Data will be electronically stored
- In the University of Manchester Drive
- Password protected
- Uses of data will be for research in PhD project

Section 12	Project team employed by the applicant organisation

Please list the name and job title of each member of the applicant organisation who will have access to the data for the purposes of this request. Please also confirm that they have a formal contract with the applicant organisation and will therefore be covered by the HQIP Data Sharing Agreement. Please add additional rows if necessary.

Where the data map in Section 11 details processing of data which is not anonymous by additional organisations, a partner organisation form is required to be completed for each.

Team member	Name	Job title	Contract in place with applicant organisation
Principal investigator	Craig Smith	Professor of Stroke medicine	☐ No ☒ Yes
Project member 1	Marco Antonio Lobo Chaves	PhD student	☐ No ☒ Yes
Project member 2	Andy Vail	Professor of Biostatistics	☐ No ☒ Yes

Project member 3	Matthew Gittins	Lecturer of Biostatistics	☐ No	☒ Yes
Project member 4	Click or tap here to enter text.	Click or tap here to enter text.	☐ No	☐ Yes
Project member 5	Click or tap here to enter text.	Click or tap here to enter text.	☐ No	☐ Yes

Section 13	Data Protection
As a data controller your organisation should be registered with the Information Commissioners Office (ICO). Please provide the following information.	

Registered name *(if different to applicant name, please state reason)*	The University of Manchester
Registration number	Z6787610
Expiry date	04/06/2021

Section 14	Legal basis (of the processing you intend to undertake)
If you are requesting data that is fully anonymous, please proceed to section 20	

GDPR Legal Basis	**Article 6 legal basis:** Section 1, paragraph E) **Justification:** processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller
	Article 9 legal basis: Section 2, paragraph J) **Justification:** Archiving, research and statistics (with a basis in law.
Common law of duty of confidentiality is addressed by	**If the data you are requesting is personally identifiable please explain how you have addressed the common law duty of confidentiality below.**
	☐ **Explicit informed consent** *(please enclose consent form and patient information sheet with this application)*
	☐ **Approval under section 251 of the NHS Act 2006** *(please enclose both the application and the approval letter)*
	The section 251 approval enables the applicant to:

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	☐ **Hold/receive personal data**	☐ **Transfer/access personal data**	☐ **Operate on and link personal data**
	☐ **Other legal basis**		
	If other legal basis selected, please provide further information here with reference to the statute, regulation or other provision relied upon: Click or tap here to enter text.		

Section 15	Fair Processing

Please describe what transparency information has been provided to the data subjects that the data requested relates to. Please ensure you enclose copies of any privacy notices and other material you rely on when submitting this application.

Information provided by the <u>HQIP project</u>	https://www.strokeaudit.org/PatientInfo.aspx
Information provided by the <u>applicant</u>	Self-funded PhD ProjectForm_CJSMITH

Section 16	Security

Each organisation processing data that is not fully anonymous as part of this project must demonstrate that they have appropriate security arrangements are in place. Please confirm whether the applicant organisation has a compliant Data Security and Protection Toolkit.
(Please note that additional organisations processing data which is not fully anonymous must complete a partner organisation form and evidence of security arrangements)

Applicant organisation *(please select one answer)*	☒ **Yes** *If yes, please provide evidence with this application.*	**ODS code**	8D594
		Status	Standards Met
		Published date	08/06/2020
	☐ **No**	**If no, please provide below alternative evidence of adequate organisational and technical measures; to ensure the security of processing and preserve the confidentiality, integrity and availability of data.**	
		Click or tap here to enter text.	

Section 17	Retention and destruction

Please state the date until which you are seeking to retain the data and the reason. *NB. That the requirement to extend the Data Sharing Agreement (if retention is requested for longer than its original term) would still apply.*	30/06/2022 It's not intended to ask for an extension, but in the event that it's required, the University Data protection officer will be consulted
Please provide details of how you intend to destroy the data at the end of the retention period.	IT services will be contacted that will delete the data using a software called Blanko, the team will provide a destruction certificate
Please confirm that you will submit a certificate of destruction to HQIP within 5 business days of destruction of the data.	☒ **Yes**

Section 18	Intention to link data
Do you intend for the requested data set to be linked with any additional data sets? If yes, please provide full details of the data controller(s) of the secondary dataset(s) and a description of which organisation will perform the linkage and how the linkage will take place. HQIP will work to the principle that other relevant requests are in process. *(Please select one answer)*	

☒ **No intended linkage**	☐ **Intention to link the data.** *Please provide full details of linkage below.*

If there is an intention to link the data, please provide full details here:

Click or tap here to enter text.

Section 19	Further information
Please use the section below to add any additional information to support your request.	

Result - Not research ethics.pdf   SSNAP statement of compliance with ISB 1   Information Commissioners - Da   Organisation Details.pdf

Section 20		Attachments Checklist						

Please use the table below to ensure that the documents / information listed are either contained within the application or submitted as attachments.

Type of data / Level of data	Applicant organisation(s)						Data provider	
	Data items spreadsheet	Evidence of Data Security and Protection (DSPT) Toolkit or equivalent	Data flow map	Ethics approval OR confirmation that it is not required	Fair processing information	Legal basis supporting evidence (such as, consent form and patient leaflet, s251 application and approval letter or any other evidence)	Description for how the data will be de-identified to reduce any risk of re-identification	Fair processing information
Anonymous	✓		✓					
De-personalised	✓	✓	✓	✓	✓	✓	✓	✓
Personally Identifiable	✓	✓	✓	✓	✓	✓		✓

Statistical code used in this thesis

```
preserve

gen dummyvariable=1

keep stroketeam_n dummyvariable s1admissionyear

collapse (sum) dummyvariable, by(stroketeam_n s1admissionyear)

list, sep(0)

gen strokecount=dummyvariable

collapse (mean) strokecount, by(stroketeam_n)

list, sep (0)

sort strokecount

gen strokecount1=strokecount if (strokecount >150)

list, sep(0)

restore


merge

*Variation SAP dofile*

preserve

drop if strokecount1==.

melogit sap7days_n i.ageonarrival i.s2rankinbeforestroke i.loc
nihssonarrivalnew_n gender_n chf_n afib_n diabetes_n htn_n
prevstroketia_n dysphagia_n|| stroketeam_n:, covariance
(unstructured) iterate (50)

estimates store m2

drop if e(sample)!=1

predict adjustedre, reffects ebmodes reses(adjustedrese)

predict adjustedfe, xb

predict adjustedfese, stdp

gen intercept=_b[_cons]

estat icc

melogit sap7days_n || stroketeam_n:, covariance (unstructured)
iterate (50)

predict unadjustedre, reffects ebmodes reses(unadjustedrese)

gen unadintercept=_b[_cons]

estat icc

collapse adjustedre adjustedrese adjustedfe adjustedfese intercept
unadjustedre unadjustedrese unadintercept, by(stroketeam_n)
```

```
list, sep(0)

gen adjlow=(adjustedre+adjustedfe)-1.96*(adjustedrese)

gen adjupp=(adjustedre+adjustedfe)+1.96*(adjustedrese)

gen adjnewprediction=1/(1+exp(-1*((adjustedre+adjustedfe))))

gen adjnewlow=1/(1+exp(-1*((adjlow))))

gen adjnewupp=1/(1+exp(-1*((adjupp))))

gen unadjlow=(unadjustedre)-1.96*(unadjustedrese)

gen unadjupp=(unadjustedre)+1.96*(unadjustedrese)

gen unadjprediction=1/(1+exp(-1*(unadintercept+unadjustedre)))

gen unadjlownew=1/(1+exp(-1*(unadintercept+unadjlow)))

gen unadjuppnew=1/(1+exp(-1*(unadintercept+unadjupp)))

summarize adjnewprediction, detail

summarize unadjprediction, detail

egen adjrank=rank(adjnewprediction), unique

egen unadjrank=rank(unadjprediction), unique

twoway (rcap adjnewlow adjnewupp adjrank) (scatter adjnewprediction
adjrank)

twoway (rcap unadjlownew unadjuppnew unadjrank) (scatter
unadjprediction unadjrank)

graph box unadjprediction adjnewprediction

restore


*Care processes dofile*

preserve

drop if strokecount1==.

gen prehospital = 0 if onsettoarrival_n<=86

replace prehospital = 1 if onsettoarrival_n>=86 &
onsettoarrival_n<=166

replace prehospital = 2 if onsettoarrival_n>=166 &
onsettoarrival_n<=510

replace prehospital = 3 if onsettoarrival_n>=510 &
onsettoarrival_n~=.

replace prehospital = 4 if onsettoarrival_n==.

generate doortostrokeunit = (onsettostrokeunit_n-onsettoarrival_n)

gen doortostrokeunitcat = 0 if doortostrokeunit<=113
```

replace doortostrokeunitcat = 1 if doortostrokeunit>=113 & doortostrokeunit<=194

replace doortostrokeunitcat = 2 if doortostrokeunit>=194 & doortostrokeunit<=305

replace doortostrokeunitcat = 3 if doortostrokeunit>=305 & doortostrokeunit~=.

replace doortostrokeunitcat = 4 if doortostrokeunit==.

generate doortoneedle = (onsettothrombolysismin_n-onsettoarrival_n)

gen doortoneedlecat = 0 if onsettothrombolysismin_n==. & thrombolysis_n<=2|doortoneedle==.

replace doortoneedlecat = 1 if doortoneedle<=37

replace doortoneedlecat = 2 if doortoneedle>=37 & doortoneedle<=53

replace doortoneedlecat = 3 if doortoneedle>=53 & doortoneedle<=77

replace doortoneedlecat = 4 if doortoneedle>=77 & doortoneedle~=.

gen strokenursecat = 0 if clckstarttostrokenurse_n<=8

replace strokenursecat = 1 if clckstarttostrokenurse_n>=8 & clckstarttostrokenurse_n<=84

replace strokenursecat = 2 if clckstarttostrokenurse_n>=84 & clckstarttostrokenurse_n<=260

replace strokenursecat = 3 if clckstarttostrokenurse_n>=260 & clckstarttostrokenurse~=.

replace strokenursecat = 4 if clckstarttostrokenurse_n==.

gen swallowscreencat = 0 if clckstarttoswalloscrn_n<=44

replace swallowscreencat = 1 if clckstarttoswalloscrn_n>=44 & clckstarttoswalloscrn_n<=84

replace swallowscreencat = 2 if clckstarttoswalloscrn_n>=84 & clckstarttoswalloscrn_n<=149

replace swallowscreencat = 3 if clckstarttoswalloscrn_n>=149 & clckstarttoswalloscrn_n~=.

replace swallowscreencat = 4 if clckstarttoswalloscrn_n==.

gen strokespecialistcat = 0 if clckstrttostrksplst_n<=120

replace strokespecialistcat = 1 if clckstrttostrksplst_n>=120 & clckstrttostrksplst_n<=694

replace strokespecialistcat = 2 if clckstrttostrksplst_n>=694 & clckstrttostrksplst_n<=1217

replace strokespecialistcat = 3 if clckstrttostrksplst_n>=1217 & clckstrttostrksplst_n~=.

replace strokespecialistcat = 4 if clckstrttostrksplst_n==.

gen physiocat = 0 if clckstarttophysio_n<=940

```
replace physiocat = 1 if clckstarttophysio_n>=940 &
clckstarttophysio_n<=1276

replace physiocat = 2 if clckstarttophysio_n>=1276 &
clckstarttophysio_n<=1665

replace physiocat = 3 if clckstarttophysio_n>=1665 &
clckstarttophysio_n~=.

replace physiocat = 4 if clckstarttophysio_n==.

gen saltcat = 0 if clckstarttoswalloassmnt_n<=350

replace saltcat = 1 if clckstarttoswalloassmnt_n>=350 &
clckstarttoswalloassmnt_n<=1182

replace saltcat = 2 if clckstarttoswalloassmnt_n>=1182 &
clckstarttoswalloassmnt_n<=1854

replace saltcat = 3 if clckstarttoswalloassmnt_n>=1854 &
clckstarttoswalloassmnt_n~=.

replace saltcat = 4 if clckstarttoswalloassmnt_n==.

gen compositenurse = 0 if strokenursecat==0 | swallowscreencat==0

replace compositenurse = 1 if clckstarttostrokenurse_n>=8 &
clckstarttostrokenurse_n<=84 | clckstarttoswalloscrn_n>=44 &
clckstarttoswalloscrn_n<=84

replace compositenurse = 2 if clckstarttostrokenurse_n>=84 &
clckstarttostrokenurse_n<=260 | clckstarttoswalloscrn_n>=84 &
clckstarttoswalloscrn_n<=149

replace compositenurse = 3 if clckstarttostrokenurse_n>=260 &
clckstarttostrokenurse~=. | clckstarttoswalloscrn_n>=149 &
clckstarttoswalloscrn_n~=.

replace compositenurse = 4 if clckstarttoswalloscrn_n==. |
clckstarttostrokenurse_n==.

gen strokeunittime = 0 if onsettostrokeunit_n<=251

replace strokeunittime = 1 if onsettostrokeunit_n>=251 &
onsettostrokeunit_n<=441

replace strokeunittime = 2 if onsettostrokeunit_n>=441 &
onsettostrokeunit_n<=1200

replace strokeunittime = 3 if onsettostrokeunit_n>=1200 &
onsettostrokeunit_n~=.

replace strokeunittime = 4 if onsettostrokeunit_n==.

tab sap7days_n prehospital, missing

tab sap7days_n doortostrokeunitcat, missing

tab sap7days_n doortoneedlecat, missing

tab sap7days_n strokenursecat, missing

tab sap7days_n swallowscreencat, missing
```

```
tab sap7days_n strokespecialistcat, missing

tab sap7days_n physiocat, missing

tab sap7days_n saltcat, missing

tab prehospital doortostrokeunitcat, missing

tab doortostrokeunitcat firstward_n, missing

tab sap7days_n strokeunittime, missing

tab sap7days_n compositenurse, missing

summarize onsettostrokeunit_n if sap7days_n==0, detail

summarize onsettostrokeunit_n if sap7days_n==1, detail

summarize clckstarttostrokenurse_n if sap7days_n==0, detail

summarize clckstarttostrokenurse_n if sap7days_n==1, detail

summarize doortoneedle if sap7days_n==0, detail

summarize doortoneedle if sap7days_n==1, detail

summarize clckstrttostrksplst_n if sap7days_n==0, detail

summarize clckstrttostrksplst_n if sap7days_n==1, detail

summarize clckstarttophysio_n if sap7days_n==0, detail

summarize clckstarttophysio_n if sap7days_n==1, detail

tab sap7days_n thrombolysis_n, missing

tab prehospital doortostrokeunitcat, missing

summarize lengthofstayindays_n if doortostrokeunitcat==4, detail

tab doortostrokeunitcat s7dischargetype if doortostrokeunitcat==4,
missing

tab doortostrokeunitcat firstwardatthishsp_n if
doortostrokeunitcat==4, missing

gen nihsscatnew = 0 if nihssonarrivalnew_n<=4

replace nihsscatnew = 1 if nihssonarrivalnew_n >=4 &
nihssonarrivalnew_n <=15

replace nihsscatnew = 2 if nihssonarrivalnew_n >=15 &
nihssonarrivalnew_n <=20

replace nihsscatnew = 3 if nihssonarrivalnew_n >=20

replace nihsscatnew = 4 if nihssonarrivalnew_n==.

summarize onsettostrokeunit_n, detail

summarize doortoneedle, detail

summarize clckstarttostrokenurse_n, detail

summarize clckstarttoswalloscrn_n, detail

summarize clckstarttophysio_n, detail
```

```
summarize clckstrttostrksplst_n, detail

tab nihsscatnew sap7days_n, missing

tab nihsscatnew physiocat, missing

tab sap7days_n physiocat, missing

tab physiocat gender_n, missing

tab physiocat chf_n, missing

tab physiocat diabetes_n, missing

tab physiocat s2rankinbeforestroke, missing

tab physiocat htn_n, missing

tab physiocat prevstroketia_n, missing

tab physiocat dysphagia_n, missing

drop if lengthofstayindays_n <7

melogit sap7days_n i.strokeunittime i.ageonarrival_n
s2rankinbeforestroke i.nihsscatnew gender_n chf_n afib_n diabetes_n
htn_n prevstroketia_n dysphagia_n|| stroketeam_n:, covariance
(unstructured) or iterate (50)

melogit sap7days_n i.strokeunittime i.doortoneedlecat
i.ageonarrival_n s2rankinbeforestroke i.nihsscatnew gender_n chf_n
afib_n diabetes_n htn_n prevstroketia_n dysphagia_n|| stroketeam_n:,
covariance (unstructured) or iterate (50)

melogit sap7days_n i.strokeunittime  i.compositenurse
i.doortoneedlecat i.ageonarrival_n s2rankinbeforestroke
i.nihsscatnew gender_n chf_n afib_n diabetes_n htn_n prevstroketia_n
dysphagia_n|| stroketeam_n:, covariance (unstructured) or iterate
(50)

melogit sap7days_n i.strokeunittime i.doortoneedlecat
i.compositenurse i.strokespecialistcat i.ageonarrival_n
s2rankinbeforestroke i.nihsscatnew gender_n chf_n afib_n diabetes_n
htn_n prevstroketia_n dysphagia_n|| stroketeam_n:, covariance
(unstructured) or iterate (50)

melogit sap7days_n i.strokeunittime i.doortoneedlecat
i.compositenurse i.strokespecialistcat i.physiocat i.ageonarrival_n
s2rankinbeforestroke i.nihsscatnew gender_n chf_n afib_n diabetes_n
htn_n prevstroketia_n dysphagia_n|| stroketeam_n:, covariance
(unstructured) or iterate (50)

restore


*Outcomes dofile*

preserve

drop if strokecount1==.

gen totallengthofstaydays = (totallengthofstay/1440)
```

```
gen totallengthofstayminus7 = (totallengthofstay-10080)

gen totallengthofstayminus7days = (totallengthofstayminus7/1440)

gen strokenursecat = 0 if clockstartstrokenurse>=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 1 if clockstartstrokenurse<=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 2 if clockstartstrokenurse==.

gen swallowscreencat = 0 if clockstartswallowscreen>240 &
clockstartswallowscreen~=.

replace swallowscreencat = 1 if clockstartswallowscreen==.

gen physiocat = 0 if clockstartphysio==.

replace physiocat = 1 if clockstartphysio

gen saltcat = 0 if clockstartswallowassessmentsalt==.

replace saltcat = 1 if clockstartswallowassessmentsalt

gen strokeunittime = 0 if onsetstrokeunit>=240 & onsetstrokeunit~=.

replace strokeunittime = 1 if onsetstrokeunit<=240 &
onsetstrokeunit~=.

replace strokeunittime = 2 if onsetstrokeunit==.

gen otcat = 0 if clockstartot==.

replace otcat = 1 if clockstartot>0 & clockstartot~=.

summarize totallengthofstaydays, detail

drop if totallengthofstaydays <7

summarize totallengthofstayminus7, detail

summarize totallengthofstayminus7 if sap7days_n==1, detail

summarize totallengthofstayminus7 if sap7days_n==2, detail

gen decade = (s1ageonarrival/10)

gen daysinteger = int(totallengthofstayminus7days)

summarize daysinteger if sap7days_n==1, detail

summarize daysinteger if sap7days_n==2, detail

tab saltcat, missing

tab physiocat, missing

tab strokenursecat, missing

tab swallowscreencat, missing

tab strokeunittime, missing

tab otcat, missing
```

```
gen physioandsaltandot = 0 if clockstartphysio==. |
clockstartswallowassessmentsalt==. | clockstartot==.

replace physioandsaltandot = 1 if clockstartphysio &
clockstartphysio~=. & clockstartswallowassessmentsalt &
clockstartswallowassessmentsalt==. & clockstartot & clockstartot~=.

recode physioandsaltandot (.=0)

tab physioandsaltandot sap7days_n, missing

drop if totallengthofstaydays >=365

menbreg daysinteger sap7days_n || teamcode:, iterate (50) irr

menbreg daysinteger sap7days_n s2rankinbeforestroke s2nihssarrival
decade chf_n afib_n htn_n diabetes_n prevstroketia_n gender_n||
teamcode:, iterate (50) irr

menbreg daysinteger sap7days_n i.strokeunittime swallowscreencat
physioandsaltandot thrombolysis_n s2rankinbeforestroke
s2nihssarrival decade chf_n htn_n afib_n diabetes_n prevstroketia_n
gender_n || teamcode:, iterate (50) irr

restore


preserve

drop if strokecount1==.

gen totallengthofstaydays = (totallengthofstay/1440)

gen totallengthofstayminus7 = (totallengthofstay-10080)

gen totallengthofstayminus7days = (totallengthofstayminus7/1440)

gen strokenursecat = 0 if clockstartstrokenurse>=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 1 if clockstartstrokenurse<=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 2 if clockstartstrokenurse==.

gen swallowscreencat = 0 if clockstartswallowscreen>240 &
clockstartswallowscreen~=.

replace swallowscreencat = 1 if clockstartswallowscreen==.

gen physiocat = 0 if clockstartphysio==.

replace physiocat = 1 if clockstartphysio

gen saltcat = 0 if clockstartswallowassessmentsalt==.

replace saltcat = 1 if clockstartswallowassessmentsalt

gen strokeunittime = 0 if onsetstrokeunit>=240 & onsetstrokeunit~=.

replace strokeunittime = 1 if onsetstrokeunit<=240 &
onsetstrokeunit~=.

replace strokeunittime = 2 if onsetstrokeunit==.
```

```stata
gen otcat = 0 if clockstartot==.

replace otcat = 1 if clockstartot>0 & clockstartot~=.

summarize totallengthofstaydays, detail

drop if totallengthofstaydays <7

summarize totallengthofstayminus7, detail

summarize totallengthofstayminus7 if sap7days_n==1, detail

summarize totallengthofstayminus7 if sap7days_n==2, detail

gen decade = (s1ageonarrival/10)

gen daysinteger = int(totallengthofstayminus7days)

summarize daysinteger if sap7days_n==1, detail

summarize daysinteger if sap7days_n==2, detail

tab saltcat, missing

tab physiocat, missing

tab strokenursecat, missing

tab swallowscreencat, missing

tab strokeunittime, missing

tab otcat, missing

gen physioandsaltandot = 0 if clockstartphysio==. |
clockstartswallowassessmentsalt==. | clockstartot==.

replace physioandsaltandot = 1 if clockstartphysio &
clockstartphysio~=. & clockstartswallowassessmentsalt &
clockstartswallowassessmentsalt==. & clockstartot & clockstartot~=.

recode physioandsaltandot (.=0)

drop if totallengthofstaydays >=365

meologit s7rankindischarge sap7days_n || teamcode:, or iterate (50)

meologit s7rankindischarge sap7days_n decade s2rankinbeforestroke
s2nihssarrival chf_n afib_n diabetes_n prevstroketia_n htn_n
gender_n|| teamcode:, or iterate (50)

meologit s7rankindischarge sap7days_n i.strokeunittime
swallowscreencat physioandsaltandot physioandsalt thrombolysis_n
decade s2rankinbeforestroke s2nihssarrival chf_n afib_n diabetes_n
prevstroketia_n htn_n gender_n|| teamcode:, or iterate (50)

restore




preserve

drop if strokecount1==.
```

```
gen totallengthofstaydays = (totallengthofstay/1440)

gen totallengthofstayminus7 = (totallengthofstay-10080)

gen totallengthofstayminus7days = (totallengthofstayminus7/1440)

gen strokenursecat = 0 if clockstartstrokenurse>=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 1 if clockstartstrokenurse<=1440 &
clockstartstrokenurse~=.

replace strokenursecat = 2 if clockstartstrokenurse==.

gen swallowscreencat = 0 if clockstartswallowscreen>240 &
clockstartswallowscreen~=.

replace swallowscreencat = 1 if clockstartswallowscreen==.

gen physiocat = 0 if clockstartphysio==.

replace physiocat = 1 if clockstartphysio

gen saltcat = 0 if clockstartswallowassessmentsalt==.

replace saltcat = 1 if clockstartswallowassessmentsalt

gen strokeunittime = 0 if onsetstrokeunit>=240 & onsetstrokeunit~=.

replace strokeunittime = 1 if onsetstrokeunit<=240 &
onsetstrokeunit~=.

replace strokeunittime = 2 if onsetstrokeunit==.

gen otcat = 0 if clockstartot==.

replace otcat = 1 if clockstartot>0 & clockstartot~=.

summarize totallengthofstaydays, detail

drop if totallengthofstaydays <7

summarize totallengthofstayminus7, detail

summarize totallengthofstayminus7 if sap7days_n==1, detail

summarize totallengthofstayminus7 if sap7days_n==2, detail

gen decade = (s1ageonarrival/10)

gen daysinteger = int(totallengthofstayminus7days)

summarize daysinteger if sap7days_n==1, detail

summarize daysinteger if sap7days_n==2, detail

tab saltcat sap7days_n, missing

tab physiocat sap7days_n, missing

tab strokenursecat sap7days_n, missing

tab swallowscreencat sap7days_n, missing

tab strokeunittime sap7days_n, missing

tab otcat sap7days_n, missing
```

```
tab thrombolysis_n sap7days_n, missing

tab gender_n sap7days_n, missing

gen staytotal = timetoinhospitaldeath

replace staytotal = totallengthofstay if staytotal==.

drop if totallengthofstaydays <7

gen inhospitaldeathdays = (timetoinhospitaldeath/1440)

gen staytotaldays = (staytotal/1440)

gen staytotalinteger = int(staytotaldays)

summarize inhospitaldeathdays, detail

summarize inhospitaldeathdays if sap7days_n==1, detail

summarize inhospitaldeathdays if sap7days_n==2, detail

gen died = dischargetype_n==1

tab sap7days_n died, missing

gen physioandsaltandot = 0 if clockstartphysio==. |
clockstartswallowassessmentsalt==. | clockstartot==.

replace physioandsaltandot = 1 if clockstartphysio &
clockstartphysio~=. & clockstartswallowassessmentsalt &
clockstartswallowassessmentsalt==. & clockstartot & clockstartot~=.

recode physioandsaltandot (.=0)

drop if staytotaldays >=365

tab physioandsaltandot sap7days_n, missing

stset staytotaldays, failure(died)

mestreg sap7days_n || teamcode:, distribution(exponential) iterate
(50)

mestreg sap7days_n decade s2rankinbeforestroke s2nihssarrival chf_n
afib_n diabetes_n htn_n prevstroketia_n gender_n|| teamcode:,
distribution(weibull) iterate (50)

mestreg sap7days_n i.strokeunittime swallowscreencat
physioandsaltandot thrombolysis_n decade s2rankinbeforestroke
s2nihssarrival chf_n afib_n diabetes_n htn_n prevstroketia_n
gender_n|| teamcode:, distribution(weibull) iterate (50)

sts graph, by(sap7days_n)

stset, clear

restore
```