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Incidence of Hospitalized Acute Lower Respiratory Tract Disease Including Pneumonia and Lower Respiratory Tract Infection in Bristol, England, 2019

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Title: Incidence of Hospitalized Acute Lower Respiratory Tract Disease Including Pneumonia and Lower Respiratory Tract Infection in Bristol, England, 2019

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3 **Competing Interests:** EB, JS, JC, SG, and BG are full time employees of Pfizer Vaccines and hold
4
5 stock or stock options. CH is Principal Investigator of the Avon CAP study
6
7 which is an investigator-led University of Bristol study funded by Pfizer and
8
9 has previously received support from the NIHR in an Academic Clinical
10
11 Fellowship. AF is a member of the Joint Committee on Vaccination and
12
13 Immunization (JCVI) and chair of the World Health Organization European
14
15 Technical Advisory Group of Experts on Immunization (ETAGE) committee. In
16
17 addition to receiving funding from Pfizer as Chief Investigator of this study,
18
19 he leads another project investigating transmission of respiratory bacteria in
20
21 families jointly funded by Pfizer and the Gates Foundation. The other
22
23 authors have no relevant conflicts of interest to declare.
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28 **Word count:** 2997/4000
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33 **Summary (38/40 words):** Using both retrospective and prospective methodologies, we found a high
34
35 annual incidence of acute lower respiratory disease (>1700 per 100000; 1.7%) in and around Bristol,
36
37 UK: pneumonia (~0.6%), lower respiratory tract infection without pneumonia (>0.7%), and heart
38
39 failure (>0.3%).
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41

42 **Author Contributions:** CH, EB, MGG, JS, BDG and AF generated the research questions and analysis
43
44 plan CH, EB, MGG, JS, JC, SG and BDG undertook and contributed to the data
45
46 analysis. AF oversaw the research and data collection which was undertaken by
47
48 CH and MGG. All authors contributed to the preparation of the manuscript.
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3 **1 Abstract (278/300):**

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5 **2 Objectives**

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8 3 To determine the disease burden of aLRTD and its subsets (pneumonia, lower respiratory tract
9 4 infection [LRTI], heart failure) in hospitalized adults in Bristol, UK.

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13 **5 Setting**

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16 6 Single-centre, secondary care hospital, Bristol UK

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19 **7 Design**

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22 8 We estimated aLRTD hospitalizations incidence in adults (≥ 18 years) in Bristol, UK using two
23 9 approaches. First, retrospective ICD-10 code analysis (first five positions/hospitalization) identified
24 10 aLRTD events over a 12-month period (March2018–Feb2019). Secondly, during a 21-day prospective
25 11 review (19Aug–9Sept2019), aLRTD admissions were identified, categorized by diagnosis, and
26 12 subsequently annualized. Hospital catchment denominators were calculated using linked general
27 13 practice and hospitalization data, with each practice's denominator contribution calculated based on
28 14 practice population and percent of the practices' hospitalizations admitted to the study hospital.

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38 **15 Participants**

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41 16 Prospective review: 1322 adults screened; 410 identified with aLRTD. Retrospective review: 7727 adult
42 17 admissions.

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46 **18 Primary and Secondary outcome measures**

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49 19 The incidence of aLRTD and its subsets in the adult population of Southmead Hospital, Bristol UK.

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52 **20 Results**

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55 21 Based on ICD-10 code analysis, annual incidences per 100000 population were: aLRTD, 1901;
56 22 pneumonia, 591; LRTI, 739; heart failure, 402. aLRTD incidence was highest among those ≥ 65 -years:
57 23 65–74 (3684 per 100000 adults), 75–84 (6962 per 100000 adults), and ≥ 85 (11430 per 100000 adults).

24 During the prospective review, 410/1322 (31%) hospitalized adults had aLRTD signs/symptoms, and
25 annualized incidences closely replicated retrospective analysis results.

26 **Conclusions**

27 aLRTD disease burden was high, increasing sharply with age. aLRTD incidence is probably higher than
28 estimated previously due to criteria specifying respiratory-specific symptoms or radiological change,
29 usage of only the first diagnosis code, and mismatch between case count sources and population
30 denominators. This may have significant consequences for healthcare planning, including usage of
31 current and future vaccinations against respiratory infection.

34 ***Strengths and Limitations of This Study***

- 35 • We used two analytical methods at the same site over a comparable period, to calculate
36 incidence using both prospective and retrospective approaches.
- 37 • The case burden of aLRTD and its subgroups was pre-defined and included patients with
38 atypical presentations
- 39 • We calculated incidence using a denominator derived from GP records, providing increased
40 accuracy compared to population calculations based on census data.
- 41 • This was a single-center study, with a predominantly Caucasian cohort; therefore, the findings
42 might not be generalizable to other populations.
- 43 • The ICD-10 coding data analysis was limited to codes within the first five positions, and
44 therefore may have excluded some cases where other diagnoses were placed higher in the
45 diagnostic coding hierarchy.

47 Introduction

48 Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, lower respiratory tract
49 infection (LRTI), acute bronchitis, exacerbation of underlying respiratory diseases, including asthma
50 and chronic obstructive pulmonary disease (COPD), and acute heart failure (HF) events resulting in
51 respiratory symptoms (e.g. breathlessness). Before the COVID-19 pandemic, European healthcare
52 costs for pneumonia alone were estimated at €10 billion annually, including €5.7 billion for inpatient
53 care. [1] Pneumonia incidence in Europe varies by country and intra-country region, age,
54 socioeconomic status, and gender; [2-4, 7] however, in all studies pneumonia incidence increases
55 sharply with age. [3] Pneumonia affects an estimated 0.5% to 1% of UK adults each year [5, 6]. Overall
56 LRTI incidence is considerably higher with ~15% of UK adults aged ≥65 years experiencing an event
57 each year. [7]

58
59 However, aLRTD incidence may be considerably higher than previously reported, given that published
60 literature has documented several reasons why previous estimates may have been erroneously low.
61 Estimates of aLRTD based on pneumonia defined as radiologically demonstrated alveolar infiltrates,
62 may underestimate true disease burden as chest radiography (CXR) is an imperfect gold-standard.
63 Immunosuppressed, elderly or dehydrated patients are likely to be under-represented if respiratory
64 infection is defined by radiologically demonstrated changes. [8, 9] Microbiological investigations for
65 pneumonia are undertaken variably and identify a causative pathogen in 50% of cases at most [10,
66 11]; hence, the disease is probably under-reported when confirmed microbiological diagnosis is
67 required. Furthermore, Respiratory Syncytial Virus (RSV) infection has recently been recognized as an
68 important respiratory pathogen later in life, [16] with severe disease occurring in patient groups in
69 whom the diagnosis is likely to be under-recognized (e.g. the elderly or those with underlying cardiac
70 conditions). [17] Studies of clinical coding data are retrospective and subject to recognized limitations
71 associated with this methodology. [12, 13] Older patients with pneumonia often have atypical

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3 72 presenting signs and symptoms, which may lead to missed or incorrect admission diagnoses. [14]
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5 73 Pneumonia may occur secondary to, or be an underlying cause of, the main presenting complaint,
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7 74 particularly in patients with cerebrovascular accidents (CVA), heart failure (HF), COPD exacerbations
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10 75 or altered consciousness levels. [15] In these scenarios, pneumonia may not be the primary
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12 76 hospitalization diagnosis code and may not even be coded as an associated diagnosis.
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18 78 Given the paucity of data supporting accurate aLRTD incidence rates and its disease subsets, we
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20 79 undertook to assess aLRTD incidence by two approaches (retrospective and prospective) in Bristol,
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22 80 UK, seeking to determine the disease burden of hospitalized aLRTD and its subgroups more accurately.
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83 **Methods**

84 *Study Design*

85 This study was conducted at a large secondary care institution in UK (North Bristol NHS Trust) with
86 specialist Respiratory Services (interstitial lung disease, pleural disease). Two approaches were
87 undertaken to estimate aLRTD incidence: (1) “retrospective analysis” of aLRTD International
88 Classification of Diseases Tenth Revision (ICD-10) diagnostic codes for an entire year; and, (2) 21-day
89 observational “prospective review” of aLRTD hospital admissions.

90 *Ethics*

91 This study was approved by North Bristol NHS Trust Research Audit Ethics Committee (CA52218).

92 *Patient and Public Involvement*

93 No patient involved.

94 *Retrospective Analysis*

95 For the retrospective analysis, all adult inpatient admissions (≥ 18 years) to the study hospital during
96 March 2018–February 2019 with aLRTD ICD-10 diagnostic codes (Supplementary data 1) in any of the
97 first 5 positions were identified and categorized into aLRTD subgroups: pneumonia, LRTI, other LRTD,
98 and HF. A mutually exclusive hierarchy was used (pneumonia, LRTI, then other LRTD) although HF
99 diagnoses could co-occur with other categories. “Other LRTD” included acute respiratory events that
100 could not definitively be placed in another category.

101 *Prospective Review*

102 Adult patients (≥ 18 years) resident within Bristol, North Somerset, and South Gloucestershire Clinical
103 Commissioning Group (CCG) referred to the Acute Medical Unit (AMU) at North Bristol NHS Trust
104 during 19th August –9th September 2019 were included. A respiratory physician (CH) reviewed
105 presenting features and investigation results for each admitted patient to determine whether aLRTD

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3 106 was present. Further medical record review was undertaken if patients had: new/worsening
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5 107 breathlessness, cough or sputum production; new or worsening peripheral oedema; pleurisy; clinical
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7 108 examination findings consistent with respiratory infection or HF; or fever attributable to suspected
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9 109 respiratory infection. Patients with non-respiratory diagnoses were excluded.
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13 110 *Prospective Review Outcome measures*

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15 111 aLRTD was considered confirmed in individuals with: new/worsening respiratory symptoms, with or
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17 112 without fever; sepsis, delirium or raised inflammatory markers attributable to likely respiratory
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19 113 infection in admitting clinical team's opinion; radiological change in keeping with infection (e.g.
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21 114 consolidation); and/or final diagnosis of LRTI, pneumonia or infective exacerbation of a chronic
22
23 115 respiratory condition. A pneumonia diagnosis was assigned if radiological changes likely due to
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25 116 infection were described by the reporting radiologist. A LRTI diagnosis was assigned if aLRTD signs and
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27 117 symptoms likely to be due to infection were present without demonstrated radiological change. A HF
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29 118 diagnosis was assigned in presence of: new/worsening breathlessness and bi-basal crepitations,
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31 119 cardiac wheeze or new/worsening bilateral pitting oedema; elevated pro-NT BNP (≥ 450 pg/mL);
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33 120 radiologist-reported radiographic changes consistent with cardiac failure; or a final consultant
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35 121 physician diagnosis of HF, cardiac failure or left-ventricular failure. When present, ≥ 1 diagnosis was
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37 122 selected.
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43 123 For both retrospective and prospective studies, pneumonia included both community and healthcare
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45 124 setting acquired cases; although, the prospective review only captured admitting diagnoses and
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47 125 pneumonias occurring later during hospitalization were not included.
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50 126 *Incidence calculations*

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53 127 Annual incidence per 100000 persons was calculated for both retrospective and prospective studies.
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55 128 Case counts from prospective review were annualized (i.e., case counts by diagnosis and overall were
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3 129 divided by the percentage of annual admissions for these diagnosis groups that occurred in this 21-
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5 130 day period in the retrospective analysis).

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8 131 *Incidence Denominators*

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11 132 To calculate appropriate population denominators for incidence calculations, aLRTD hospital
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13 133 admission event data were linked to aggregated GP practice patient registration data within the NHS
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15 134 Bristol, North Somerset, and South Gloucestershire CCG for 2017–2019. Only 4% of patients sought
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17 135 care at North Bristol NHS Trust hospital from outside these local CCGs, despite presence of specialist
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19 136 respiratory services. For GP practices within these same CCGs, the proportion of their aLRTD
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21 137 admissions occurring at North Bristol NHS Trust was multiplied by their patient registration count in
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23 138 2019 by age group, to get each practice's contribution to the denominator (e.g. if 50% aLRTD
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25 139 admissions were at North Bristol among persons 50–64 years, the practice would contribute half of
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27 140 their patients 50–64 years to the denominator). Further details of this methodology have been
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29 141 described previously. [27]

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37 143 *Statistical analysis*

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40 144 Patient characteristics were tabulated by aLRTD diagnosis. Categorical variables were presented as
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42 145 counts with percentages. Continuous data are presented with means and standard deviations (SD) if
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44 146 normally distributed and medians and interquartile range (IQR) if not normally distributed. Patient
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46 147 groups difference were evaluated using the Friedman test with Wilcoxon signed-rank test.

149 **Results**

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151 *Retrospective analysis*

152 Over a 12-month period, we identified 7727 hospital admissions for aLRTD: 3005 LRTI admissions,
153 2402 pneumonia, 1633 HF and 1071 other LRTD (Table 1). aLRTD admissions were lowest in March
154 and April and highest December through February (Figure 1A), overall and for all aLRTD subgroups
155 ($P<0.05$) (Figure 1B-D). Overall, 28.1% (2244) cases were identified as being potentially hospital-
156 acquired infection based on co-occurring ICD-10 code 'Y95 Nosocomial Infection'.

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158 *Prospective review*

159 Among 1322 eligible adult patients referred to AMU over the 21-day review period (Figure 2), 410
160 patients had signs or symptoms of aLRTD: 188 (46%) LRTI; 152 (37%) pneumonia, and 77 (19%) HF.
161 Seven patients had both decompensated HF and a respiratory infection at hospital admission. On
162 admission, >10% of aLRTD patients did not have respiratory symptoms: 16 (11%) pneumonia, 25 (13%)
163 LRTI, and 18 (14%) HF (Table 2).

164 Almost all adults admitted with aLRTD underwent routine biochemistry, hematology, and radiological
165 investigation (99.9%, $n=409$). In contrast, only 150 (37%) patients with aLRTD had microbiological
166 testing performed: blood cultures ($n=149$, 36%) and urine cultures ($n=143$, 35%). Pneumonia patients
167 more commonly underwent microbiological investigation than LRTI patients ($P<0.05$) with highest
168 disparity in rates of sputum culture, urinary antigens, and respiratory viral PCR (Table 2). All cardiac
169 failure patients who underwent microbiological investigation had concomitant respiratory infection
170 (Table 2). Overall, a microbiological diagnosis was found in 11 (3%) cases, highlighting the low
171 frequency of definitive pathogen identification in aLRTD. Younger patients underwent microbiological
172 testing more frequently than the elderly for all aLRTD categories (Table 2).

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3 174 *Disease incidence*
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6 175 Retrospective analysis yielded an overall aLRTD incidence of 1901 per 100000. Disease incidence rose
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8 176 with increasing age (Table 3), both overall and for all disease subgroups; incidences per 100000 among
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10 177 adults aged ≥ 85 years were: 11430 (aLRTD), 6116 (LRTI), 4215 (pneumonia) and 4005 (HF). Overall,
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12 178 28.1% aLRTD hospitalizations also included an ICD-10 discharge code for 'nosocomial infection',
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14 179 suggesting the aLRTD event or other infection was hospital-acquired. For pneumonia 25.3% had the
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16 180 nosocomial infection code. If all of these were related to the pneumonia diagnosis, an estimated
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18 181 residual 1794 events would have been community-acquired pneumonia (annual incidence
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20 182 441/100000 adults). Among older age categories, where the incidence of aLRTD was highest, LRTI
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22 183 incidence was similar to pneumonia incidence, with an approximate 1:1 ratio of LRTI to pneumonia
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24 184 cases. However, among adults under age 50 years, there were approximately twice as many LRTI cases
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26 185 observed as pneumonia cases. Incidence calculations using annualized prospective review results
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28 186 were broadly comparable with retrospective analysis of ICD-10 data (Table 3).
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Discussion:

This is the first UK study to assess aLRTD incidence comprehensively. We conducted an analysis of 12-months of hospital admissions by ICD-10 diagnosis code data and a 21-day prospective review at a large academic hospital in southwest England. With both approaches, we found a high annual incidence of aLRTD (>1700 per 100000; 1.7%), pneumonia (~0.6%), LRTI without pneumonia (>0.7%), and HF (>0.4%). Incidences increased sharply in a non-linear manner as age increased above 65 years for all aLRTD categories. These results suggest rates are probably significantly higher than previous disease estimates from the UK (Table 4) but comparable with many results globally, [18,19] with important consequences for healthcare resources. For example, a recent review highlighted that pneumonia incidences ranged from 1000 to 2500 per 100000 (1–2.5%) among persons aged 65–74 years in Spain, Germany, France, Japan and the US, which are comparable to the >1250 per 100000 (1.3%) reported here. Some of the potential sources of underestimation for other UK incidence studies (Table 4) include: case source and denominator mismatch; use of first position in ICD-code analysis only; inclusion of enrolled subjects in consent-based prospective studies only; requiring specific symptoms and chest x-ray confirmation in order to be classified as pneumonia/aLRTD; and, lastly, the rising incidence of aLRTD.

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Comparison with published literature

No studies have reported aLRTD incidence comprehensively in UK hospitalized patients within the last 20 years. However, eight publications report incidence of ≥ 1 aLRTD subgroup. Seven publications reported community-acquired pneumonia (CAP) incidence (three from Nottingham, UK). For pneumonia, our incidence estimates were three to four-fold higher than other UK inpatient incidence estimates (Table 4) but comparable to estimates from other countries. [18, 19] Only two UK studies from approximately 20 years ago reported LRTI incidence (one with both CAP and LRTIs; Table 4), and only one provided an inpatient estimate. [25] LRTI incidence was approximately 2-fold lower than that

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3 213 calculated here, taking into account inclusion of CAP and other LRTI in their estimates. [25] The one
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5 214 UK study reporting HF incidence had methodological differences (i.e., inclusion of outpatients and
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7 215 limiting to initial HF diagnosis) and estimates could not be compared. [26] Close examination of the
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9 216 existing literature methods yielded multiple sources for potential underestimation.

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13 217 First, for incidence studies that were not countrywide, identifying an appropriate denominator is
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15 218 challenging. Like many other inpatient settings worldwide, UK hospitals' catchment areas for acute
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17 219 treatment are principally driven by geography, but the proportion of any area's residents expected to
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19 220 use the hospital becomes less clear as distance from the hospital increases because catchment areas
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21 221 and populations of different hospitals may overlap. Defining hospital catchment populations based
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23 222 solely on census data cannot account for this variability. Including all geographic areas using the
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25 223 hospital to any extent results in population denominator overestimation and underestimated
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27 224 incidence. Here, we addressed this by calculating population denominators based on hospital
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29 225 utilization behavior from referring General Practices.

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33 226 Second, other studies used fewer codes in their ICD code analysis: all limited their analyses to events
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35 227 where the diagnostic code was in the first position (Table 4; case definition column), potentially
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37 228 excluding admissions in which pneumonia/LRTI complicated other underlying respiratory diseases,
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39 229 including COPD and asthma. Limiting to first position has been shown to reduce sensitivity for
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41 230 pneumonia events by about 30% (66%–72% sensitive). [20, 21] Conversely, the recent British Thoracic
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43 231 Society (BTS) audit on CAP found ~27% of pneumonia events identified by ICD code (J12-18) had no
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45 232 new CXR infiltrates. [6] Even accounting for this potential over coding practice, our estimates remain
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47 233 well above other published UK estimates.

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52 234 Third, for other prospective studies, exclusion of events where patients did not consent to
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54 235 participation or were not identified by study surveillance processes (often conducted predominately
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56 236 during business hours) can introduce underestimation. Further, other prospective pneumonia studies
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58 237 specifically required documentation of specific symptoms, radiological findings, and treatments, [22]
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3 238 potentially excluding those without these features documented in medical records. In our prospective
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5 239 review, approximately 11% did not display typical signs and symptoms of pneumonia and could have
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7 240 been excluded by that requirement. Requiring CXR confirmation has been shown to reduce incidence
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9 241 estimates for pneumonia, [19] although all pneumonia events in our prospective review were
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12 242 radiologically confirmed.

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15 243 Fourth, trends over time may also contribute to our estimates being higher than previous reports. Our
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17 244 study's estimates are recent, and rising incidence of pneumonia has been documented in all studies
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19 245 that have reported such trends. [22-24]

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22 246 Finally, this study included, in part, hospital-acquired pneumonias (HAP), which were excluded from
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24 247 estimates calculated in some other studies (Table 4). The retrospective analysis may have included
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26 248 more nosocomial infection than the prospective review, as the latter was focused on evaluation of
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28 249 patients at admission for aLRTD and would not have reliably captured events that developed during
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31 250 hospitalization. 25.3% pneumonia events included a nosocomial infection code, but this code could
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33 251 relate to any nosocomial infection during that hospitalization. If all these cases were assumed to be
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35 252 hospital-acquired pneumonia, our estimates community-acquired pneumonia incidence would still be
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37 253 well above prior UK estimates: 441/100000 (≥ 18 years).

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41 254 While not impacting all-cause aLRTD incidence estimates discussed above, during the prospective
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43 255 review, we found low rates of microbial investigation which prevented us from generating pathogen-
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45 256 specific incidence estimates. Only 52% of patients with radiologically-confirmed pneumonia
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47 257 underwent microbiological testing during hospitalization, with even lower rates in other aLRTD
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49 258 subgroups (41% LRTI and 14% HF). Microbiological testing occurred less frequently as age increased,
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51 259 particularly in LRTI patients. It is possible that, because aLRTD hospitalizations are substantially more
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53 260 common among older persons, less etiologic investigation is performed. Furthermore, clinicians may
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55 261 elect to treat elderly patients with a more pragmatic and less invasive approach. Management
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57 262 guidelines do not require specific pathogen identification to inform treatment choice. Presence only
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3 263 of atypical features on presentation (in this series, 13% LRTI and 11% pneumonia cases) may also
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5 264 reduce the likelihood of timely microbiological testing. Low rates of microbiological testing, and
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7 265 consequently of confirmed microbiological diagnosis, may represent a source of underestimation of
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9 266 pathogen-specific disease incidence in patient groups (i.e., testing bias), particularly in elderly patient
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11 267 groups.
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17 18 269 *Strengths and Limitations of This Study*

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21 270 This study has many strengths. First, this study used two analytical methods at the same site over a
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23 271 comparable period, to calculate incidence using both prospective and retrospective approaches.
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25 272 Second, the case burden of aLRTD and its subgroups was pre-defined and included patients with
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27 273 atypical presentations but with clinical and/or radiological diagnoses, who may otherwise have been
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29 274 excluded from analysis. Additionally, we calculated incidence using a denominator derived from GP
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31 275 records, providing increased accuracy compared to population calculations based on census data.
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35 276 However, the study also had some limitations. This was a single-center study, with a predominantly
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37 277 Caucasian cohort; therefore, the findings might not be generalizable to other populations. The ICD-10
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39 278 coding data analysis was limited to codes within the first five positions, and therefore may have
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41 279 excluded some cases where other diagnoses were placed higher in the diagnostic coding hierarchy.
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43 280 Furthermore, we could not determine how many cases of the 28.1% ICD-10 cases also coded with
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45 281 nosocomial infection had hospital-acquired respiratory infection rather than other nosocomial
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47 282 infections.
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51 283 Although the denominator used to calculate incidence was derived from GP records, this was still an
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53 284 estimate as there is no precisely defined denominator hospital catchment. We were unable to exclude
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55 285 patients from outside the local CCGs in the retrospective analysis, due to the way ICD-10 data was
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57 286 obtained. However, these patients were excluded from the prospective review and the incidence
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3 287 calculated was comparable, suggesting any effect that patients attending North Bristol NHS Trust from
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5 288 outside the local CCGs have on incidence estimates is minimal. This may be because any effect of
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7 289 travelling or health-seeking behavior is bi-directional: whilst some patients admitted to Southmead
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9 290 hospital were from outside the local area, it is also true that patients with aLRTD within the relevant
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11 291 CCGs would have been admitted to other hospitals. We also acknowledge the 21-day prospective
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13 292 review period was relatively short, not repeated and may not be fully representative of clinical practice
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15 293 and cases throughout the year.
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295 In conclusion, we found similarly high estimates of LRTD incidence using two different approaches.
296 Combining all types of LRTD highlights the high burden for this important and potentially life-
297 threatening disease group. Incidence assessments require close assessments of potential areas of
298 under ascertainment, including unidentified or unenrolled cases in prospective studies, reduced
299 positions or number of ICD-10 codes included for retrospective studies, and population denominator
300 mismatch for all study types. Our prospective review findings highlight the need to consider atypical
301 clinical presentations for pneumonia and the lack of routine microbiological investigation in many
302 aLRTD patients required for pathogen-specific aLRTD incidence calculation. Future research should
303 include a fully prospective assessment of aLRTD incidence with comprehensive diagnostic testing
304 across multiple respiratory seasons, to ensure accurate capture of all aLRTD events, particularly in the
305 elderly. Such research should be undertaken given the high and rising aLRTD burden to enable
306 appropriate healthcare planning and identification of interventions which may reduce disease burden.
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8
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13 313 Harvey Walsh Limited.
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18 315 **Data Sharing**
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20 316 No additional data available
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Table 1: Demographic Characteristics of Patients admitted with aLRTD for 1 Year ICD-10 code Retrospective Analysis and 21-day Prospective Review Period -
- 2018–2019

Characteristic	Pneumonia		LRTI		Heart Failure		Other LRTD	All LRTD	
	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Retrospective Review Only	Prospective review	Retrospective analysis
N	152	2402	188	3005	77	1633	1071	410	7727
Gender, females	61 (40)	1078 (45)	99 (53)	1482 (49)	39 (51)	731 (45)	489 (46)	194 (47)	3780 (49)
Age									
Median (IQR), y	80 (67-86)	81 (66-88)	70 (46-87)	69 (45-87)	87 (72-90)	87 (70-90)	74 (53-82)	80 (64-88)	81 (65-90)
18-24	4 (3)	72 (3)	9 (5)	151 (5)	0 (0)	0 (0)	26 (2)	13 (3)	249 (3)
25-34	2 (2)	48 (2)	12 (6)	183 (6)	0 (0)	3 (0)	33 (3)	14 (3)	267 (3)
35-44	6 (4)	97 (4)	14 (7)	209 (7)	2 (3)	10 (1)	59 (6)	22 (5)	375 (5)
45-54	8 (5)	118 (5)	11 (6)	183 (6)	0 (0)	22 (1)	112 (10)	19 (5)	435 (6)
55-64	18 (12)	293 (12)	19 (10)	305 (10)	8 (10)	158 (10)	210 (20)	45 (11)	966 (13)
65-74	34 (22)	501 (21)	32 (17)	549 (18)	10 (15)	199 (12)	223 (21)	75 (18)	1472 (19)
75-84	44 (28)	667 (28)	40 (21)	621 (21)	20 (30)	498 (31)	205 (19)	100 (24)	1991 (26)
≥85	38 (26)	606 (25)	51 (27)	704 (23)	37 (55)	742 (45)	203 (19)	123 (30)	2255 (29)

Table 2. Clinical Characteristics and Investigations of Patients admitted with aLRTD over 21-day Prospective Review Period in August-September 2020

Characteristic	Pneumonia n=152 (%)	LRTI n=188 (%)	Heart Failure n=77 (%)	All LRTD n=410 (%)
GP	56 (37)	72 (39)	30 (39)	158 (39)
A&E department	93 (61)	100 (54)	45 (58)	238 (58)
Transfer from another unit	2 (1)	13 (7)	0 (0)	15 (4)
Other	1 (1)	1 (1)	2 (3)	4 (1)
Referral Source				
Typical features†	136 (89)	163 (87)	63 (82)	355 (87)
Atypical features	16 (11)	25 (13)	14 (18)	55 (13)
- collapse/falls	11 (7)	12 (6)	0 (0)	23 (6)
- confusion	0 (0)	7 (4)	4 (5)	10 (2)
- drowsiness	1 (1)	1 (1)	2 (3)	4 (1)
- off legs/generally unwell	5 (3)	5 (3)	8 (10)	18 (4)
LRTD Signs and symptoms on referral to AMU				
Biochemistry	152 (100)	185 (99)	77 (100)	419 (100)
Haematology	152 (100)	185 (99)	77 (100)	419 (100)
Radiology	152 (100)	185 (99)	77 (100)	419 (100)
Investigations Performed				
<i>Testing by Age Group</i>				
All patients	79/152 (52)*	77/188 (41)	11/77 (14)	167 (41)
18-24	3/4 (75)	6/9 (66)	0/0 (0)	9/13 (69)
25-34	0/0 (0)	6/12 (50)	0/0 (0)	6/12 (50)
35-44	5/6 (83)	10/14 (71)	2/2 (100)	17/22 (77)
45-54	6/8 (75)	6/11 (55)	0/0 (0)	13/19 (68)
55-64	11/18 (61)	12/19 (63)	5/8 (63)	31/45 (69)
65-74	15/34 (44)	12/32 (38)	1/10 (10)	28/75 (37)
75-84	21/43 (49)	10/40 (25)	2/20 (10)	33/100 (33)
≥85	18/39 (46)	15/51 (19)	1/37 (3)	34/124 (27)
Test performed				
Blood culture	79 (52)	70 (37)	5 (6)	150 (37)
Urine culture	66 (43)	77 (41)	11 (14)	150 (37)
Sputum culture	27 (18)*	7 (4)	2 (3)	35 (9)
BinaxNOW® Pn UAT ‡	29 (19)*	6 (3)	0 (0)	35 (9)
Respiratory virus PCR	16 (11)*	11 (6)	1 (1)	28 (7)
Pleural fluid culture	3 (2)	0 (0)	1 (1)	4 (1)

A&E, Accident and Emergency department; GP, general practitioner; LRTD, lower respiratory tract disease; LRTI, lower respiratory tract infection; IQR, interquartile range; Pn UAT, pneumococcal urinary antigen test; PCR, polymerase chain reaction.

* $P < 0.05$.

† Typical symptoms included cough, breathlessness, increased or discolored sputum production, wheeze, pleurisy, peripheral oedema, haemoptysis, reduced exercise tolerance and/or fever.

‡ BinaxNOW Pn UAT was only performed in accordance with NICE/BTS guidelines.

Table 3: Incidence of aLRTD resulting in hospital admission based on prospective and retrospective approaches by age group and condition, North Bristol National Health Service Trust— United Kingdom 2018–2019.

	Age Groups					
	All Adults	18-49 y	50-64 y	65-74 y	75-84 y	≥85 y
Population in 2018	406481	226920	91534	45705	29487	12835
Retrospective Analysis of a Year's ICD-10 codes						
Annual cases – N (row %)						
All aLRTD	7,727	1,130 (14)	1,103 (14)	1,684 (22)	2,053 (27)	1,757 (23)
Pneumonia	2,402	264 (11)	288 (12)	589 (25)	720 (30)	541 (22)
LRTI	3,005	576 (19)	410 (14)	572 (19)	662 (22)	785 (26)
Other LRTD	1,071	246 (23)	268 (25)	226 (21)	200 (19)	131 (12)
Heart Failure	1,633	48 (3)	189 (12)	397 (24)	485 (30)	514 (31)
LRTI/Pneumonia Ratio	1.3	2.2	1.4	1.0	0.9	1.5
Incidence (per 100,000)						
All aLRTD	1,901	497	1,205	3,684	6,962	13,689
Pneumonia	591	116	315	1,289	2,442	4,215
LRTI	739	254	448	1,252	2,245	6,116
Other LRTD	263	108	293	494	678	1,021
Heart Failure	402	21	206	869	1,645	4,005
21-day Prospective Review (annualized)						
Annualized cases – N (row %)						
All aLRTD	7,885	1,038	962	1,692	2,231	1,962
Pneumonia	2,621	224	397	776	690	534
LRTI	3,857	796	531	653	1,061	816
Heart Failure	2,000	51	205	308	641	795
LRTI/Pneumonia Ratio	1.5	3.6	1.3	0.8	1.5	1.5
Incidence (per 100,000)						
All aLRTD	1,940	458	1,050	3,703	7,565	15,283
Pneumonia	645	99	433	1,698	2,339	4,164
LRTI	944	351	580	1,429	3,599	6,360
Heart Failure	492	23	224	673	2,174	6,193

LRTI = lower respiratory tract infection; LRTD = lower respiratory tract disease.

Pneumonia category includes community and healthcare acquired. For retrospective ICD-10 based cohort, the following mutually exclusive hierarchy was used to define pneumonia, LRTI, and other LRTD; heart failure event could overlap with other categories. "Other LRTD" contains LRTD events that could not definitively be placed in one of the other respiratory disease categories.

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5 **Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North**
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7 **Bristol National Health Service Trust— United Kingdom 2018–2019.**
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10 Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower
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12 Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Lower Respiratory
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14 Tract Infection (LRTI) (white bars), (D) Other LRTD (cross-hash bars), and (E) Heart Failure (grey bars).
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19 **Figure 2: Flow diagram of the Prospective Review**
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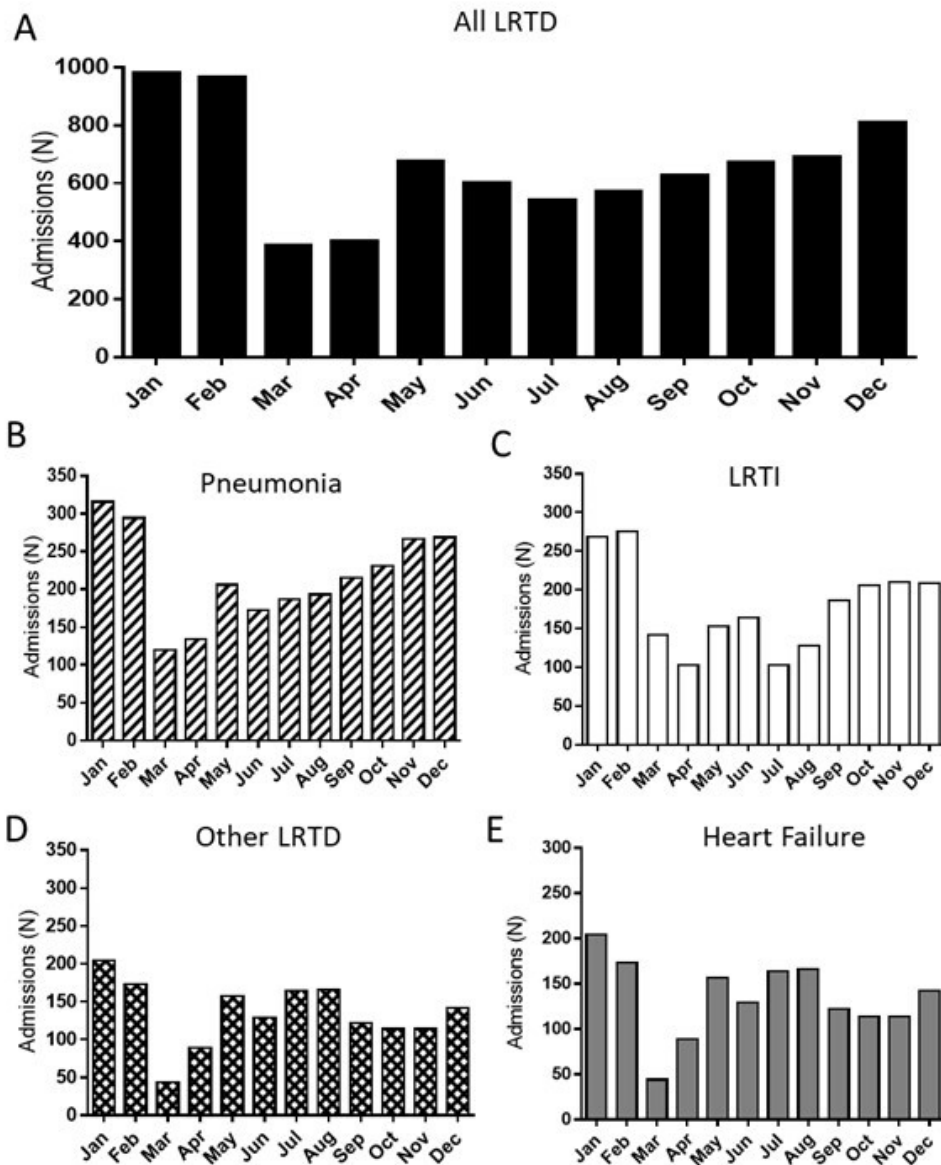


Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North Bristol National Health Service Trust— United Kingdom 2018–2019. Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Lower Respiratory Tract Infection (LRTI) (white bars), (D) Other LRTD (cross-hash bars), and (E) Heart Failure (grey bars).

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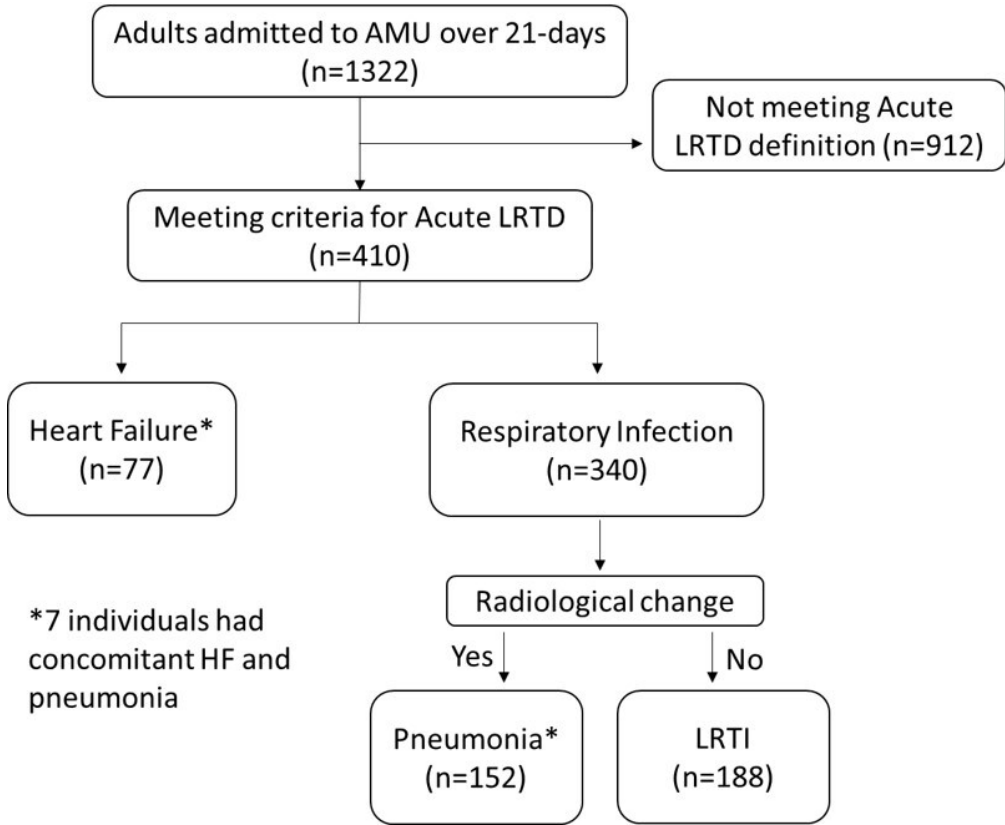


Figure 2: Flow diagram of the Prospective Review

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Table 4: Literature review of aLRTD incidence in hospitalized adults, United Kingdom

Study	Study Years	Location (Facility)	Event Setting	Age	Case Definition ^b	Key inclusion	Denominator Source	Overall Incidence	Age Breakdown (years)	Incidence per 100,000 by age ^d	Comments
Community –acquired Pneumonia											
Current Study	2018 – 2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms with radiological change in keeping with infection (prospective review portion) AND Retrospective ICD-10 code analysis (1 st 5 positions): J12-J18, J85, and J86	Hospital-acquired pneumonia (HAP) included	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	648 591	18 –49 50 –64 65 –74 75 –84 ≥85	116 315 1,289 2,442 4,215	Retrospective analysis includes 1 st 5 positions
Elston 2012, Epidemiol Infect	2002 – 2009	Hull and East Yorkshire Hospitals ^c	Inpatients only	≥16 y	ICD-10 codes (1 st position only): J18.0, J18.9, J13X, J18.1, and J15X	HAP included	Mid-year population estimates for Hull (city) and EroY (Surrounding County) from Office for National Statistics	143 (2002) – 207 (2009)	15 –64 ≥65	48.8 – 84.1 543 – 781	Fewer ICD-10 codes included than other analyses; Y95 Nosocomial infection included.
Millet 2013, J Clin Epidemiol	1997 – 2011	UK	Both inpatients and outpatients	≥65 y	Read and ICD 10 codes; no specified codes provided. For ICD-10, used first diagnosis code for first episode of hospitalization only.	HAP Excluded	Mid-year UK population estimates from Office for National Statistics	799	65 –69 70 –74 75 –79 80 –84 y 85 –89 ≥90	281 431 694 1,205 2,184 4,194	Incidence estimates converted to per 100,000 person-years
Pick 2020, Thorax ^a	2013 – 2014 2017 – 2018	Nottingham (2 large university hospitals)	Inpatients only	≥16 y	Inclusion criteria: one or more symptom suggestive of LRTI (defined as cough, increasing dyspnea, sputum production and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP Exclusion criteria: hospitalization within 10 days of index admission, a diagnosis of tuberculosis or post-obstructive pneumonia.	HAP Excluded	Mid-year estimates for the Greater Nottingham area from the Office for National Statistics, including local population data stratified by age group	96.3 158.4	16 –49 50 –64 65 –74 75 –84 ≥85 16 –49 50 –64	27.3 80.2 181.3 400.6 707.5 29.9 146.9	Only consented/enrolled subjects included in estimates Required CXR - confirmation but not all LRTI patients had CXR Census-derived denominator that may not have fully matched catchment area.

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	2013 – 2018							120.4	65 –74 75 –84 ≥85	310.4 559.5 1522.6	Required specific symptoms and evidence of treatment and some CAP events may not have had this information documented
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Thorrington 2019, BMC Med	2004 – 2005 2014 – 2015	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J18 (pneumonia of unspecified causative organism)	HAP Included	Mid-year population estimates for England for 2004 to 2015 from Office for National Statistics	NA	≥65	829	Incidence is per 100,000 person-years. Fewer ICD-10 codes included than other analyses
									≥65	1787	
Trotter 2008, EID	1997 – 1998 2004 – 2005	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J12 – J18	HAP Included	Mid-year population estimates for England for 1997 to 2004 from the Office for National Statistics	NA	65 –74 75 –84 ≥85	263 684 1599	Incidence estimates converted to 100,000 population
									65 –74	355	
									75 –84	877	
									≥85	2218	
Lower Respiratory Tract Infection						Pneumonia					
Current Study	2018 – 2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change AND Retrospective ICD-10 code analysis: J09, J10, J11; J20, J21, J22, J40, J41, J42, J44, J45, and J46	Excludes all Pneumonia	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	802 739	18 –49 50 –64 65 –74 75 –84 ≥85	254 448 1,252 2,442 6,116	
Lovering 2001, Clinical Micro. & Infection	1994 – 1996	Bristol (Southmead Hospital)	Inpatients only	≥16 y	LRTI episodes from four groups by ICD 9/10 codes: (1) CAP; (2) chest infection or acute exacerbation in presence of asthma; (3) chest infection or acute exacerbation in presence of COPD; or (4) bronchitis with no radiological evidence of pneumonia or pre-existing respiratory disease, such as COPD or asthma. No specified codes provided.	Includes Community-acquired Pneumonia HAP Excluded	No information on denominator provided	623	16 –39 40 –49 50 –59 60 –69 70 –79 >79	151 175 294 1,086 2,135 3,141	Incidence converted to per 100,000 population Study involved single hospital and no mention of source of denominator mentioned.
Millet	1997 –	UK	Both	≥65 y	Read and ICD 10 codes; no specified	Includes	Mid-year UK population	12,293	65 –69	9,221	Incidence

2013, J Clin Epidemiol	2011		inpatients and outpatients		codes provided. For ICD-10, used first diagnosis code for inpatient episode only.	Community-acquired Pneumonia HAP Excluded	estimates from Office for National Statistics. (Patients were not considered at risk for community-acquired LRTI during an LRTI illness-episode, during a HES hospitalization, or for 14 days after any HES hospitalization or CPRD hospital code. This person-time was excluded from denominator.)		70–74 75–79 80–84 85–89 ≥90	10,740 12,607 15,137 18,791 26,287	converted to per 100,000 person years
All or First Episode											
Heart Failure											
Current Study	2018-2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change AND Retrospective ICD-10 code analysis: I110; I130; I132; I50	All	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	328 402	18–49 50–64 65–74 75–84 ≥85	21 206 869 1,645 4,005	
Uijl 2019, Eur J Heart Fail	2000–2010	UK	Both inpatients and outpatients	≥55 y	4 sources of HER were linked: CPRD primary care records, HES secondary care hospital charges, Myocardial Ischaemia National Audit Project (MINAP) disease registry, and ONS national death registry. HES ICD-10 codes: Heart failure: I110, I130, I132, I260, I50 and I21. Individuals were excluded if they presented a history of HF before their index date in CPRD, HES or MINAP.	First episode at 55 years or older counted	Not Reported	Not Reported	55–64, M 55–64, F 65–74, M 65–74, F >75, M >75, F	360 190 1,360 920 3,440 2,800	Incidence converted to per 100,000 person years Included first episode of HF (inpatient or outpatient) at age 55 and up, so repeat episodes not included.

^a Only the most recent incidence estimates from the Nottingham CAP study were included.

^b Add text names for all listed ICD codes in this footnote or appendix.

^c Included hospitals were Hull Royal Infirmary, Castle Hill Hospital, Princess Royal Hospital, Scarborough District General Hospital, Bridlington & District Hospital, York Teaching Hospital, Scunthorpe General Hospital, Goole & District Hospital.

^d For the current study, only age-group estimates from the retrospective analysis were included in this table, but these were closely comparable to the annualized incidence estimates based on the prospective review. See Table 3 for full results.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 21-24
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	24
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21-24
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10-11, 21-24
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 21-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Incidence of Hospitalized Acute Lower Respiratory Tract Disease Including Pneumonia and Lower Respiratory Tract Infection in Bristol, England, 2019

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Title: Incidence of Hospitalized Acute Lower Respiratory Tract Disease Including Pneumonia and Lower Respiratory Tract Infection in Bristol, England, 2019

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1
2
3 **Competing Interests:** EB, JS, JC, SG, and BG are full time employees of Pfizer Vaccines and hold
4
5 stock or stock options. CH is Principal Investigator of the Avon CAP study
6
7 which is an investigator-led University of Bristol study funded by Pfizer and
8
9 has previously received support from the NIHR in an Academic Clinical
10
11 Fellowship. AF is a member of the Joint Committee on Vaccination and
12
13 Immunization (JCVI) and chair of the World Health Organization European
14
15 Technical Advisory Group of Experts on Immunization (ETAGE) committee. In
16
17 addition to receiving funding from Pfizer as Chief Investigator of this study,
18
19 he leads another project investigating transmission of respiratory bacteria in
20
21 families jointly funded by Pfizer and the Gates Foundation. The other
22
23 authors have no relevant conflicts of interest to declare.
24
25
26
27

28 **Word count:** 2997/4000
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30
31
32

33 **Summary (38/40 words):** Using both retrospective and prospective methodologies, we found a high
34
35 annual incidence of acute lower respiratory disease (>1700 per 100000; 1.7%) in and around Bristol,
36
37 UK: pneumonia (~0.6%), lower respiratory tract infection without pneumonia (>0.7%), and heart
38
39 failure (>0.3%).
40
41

42 **Author Contributions:** CH, EB, MGG, JS, BDG and AF generated the research questions and analysis
43
44 plan CH, EB, MGG, JS, JC, SG and BDG undertook and contributed to the data
45
46 analysis. AF oversaw the research and data collection which was undertaken by
47
48 CH and MGG. All authors contributed to the preparation of the manuscript.
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3 **1 Abstract (278/300):**

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5 **2 Objectives**

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8 3 To determine the disease burden of acute lower respiratory tract disease (aLRTD) and its subsets
9
10 4 (pneumonia, lower respiratory tract infection [LRTI], heart failure) in hospitalized adults in Bristol, UK.

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13 **5 Setting**

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16 6 Single-centre, secondary care hospital, Bristol UK

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19 **7 Design**

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21
22 8 We estimated aLRTD hospitalizations incidence in adults (≥ 18 years) in Bristol, UK using two
23
24 9 approaches. First, retrospective ICD-10 code analysis (first five positions/hospitalization) identified
25
26 10 aLRTD events over a 12-month period (March2018–Feb2019). Secondly, during a 21-day prospective
27
28 11 review (19Aug–9Sept2019), aLRTD admissions were identified, categorized by diagnosis, and
29
30 12 subsequently annualized. Hospital catchment denominators were calculated using linked general
31
32 13 practice and hospitalization data, with each practice's denominator contribution calculated based on
33
34 14 practice population and percent of the practices' hospitalizations admitted to the study hospital.

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38 **15 Participants**

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41 16 Prospective review: 1322 adults screened; 410 identified with aLRTD. Retrospective review: 7727 adult
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43 17 admissions.

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46 **18 Primary and Secondary outcome measures**

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48
49 19 The incidence of aLRTD and its subsets in the adult population of Southmead Hospital, Bristol UK.

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52 **20 Results**

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55 21 Based on ICD-10 code analysis, annual incidences per 100000 population were: aLRTD, 1901;
56
57 22 pneumonia, 591; LRTI, 739; heart failure, 402. aLRTD incidence was highest among those ≥ 65 -years:
58
59 23 65–74 (3684 per 100000 adults), 75–84 (6962 per 100000 adults), and ≥ 85 (11430 per 100000 adults).

24 During the prospective review, 410/1322 (31%) hospitalized adults had aLRTD signs/symptoms, and
25 annualized incidences closely replicated retrospective analysis results.

26 **Conclusions**

27 aLRTD disease burden was high, increasing sharply with age. aLRTD incidence is probably higher than
28 estimated previously due to criteria specifying respiratory-specific symptoms or radiological change,
29 usage of only the first diagnosis code, and mismatch between case count sources and population
30 denominators. This may have significant consequences for healthcare planning, including usage of
31 current and future vaccinations against respiratory infection.

34 ***Strengths and Limitations of This Study***

- 35 • We used two analytical methods at the same site over a comparable period, to calculate
36 incidence using both prospective and retrospective approaches.
- 37 • The case burden of aLRTD and its subgroups was pre-defined and included patients with
38 atypical presentations
- 39 • We calculated incidence using a denominator derived from GP records, providing increased
40 accuracy compared to population calculations based on census data.
- 41 • This was a single-center study, with a predominantly Caucasian cohort; therefore, the findings
42 might not be generalizable to other populations.
- 43 • The ICD-10 coding data analysis was limited to codes within the first five positions, and
44 therefore may have excluded some cases where other diagnoses were placed higher in the
45 diagnostic coding hierarchy.

47 Introduction

48 Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, non-pneumonic lower
49 respiratory tract infection (NP-LRTI), acute bronchitis, exacerbation of underlying respiratory diseases
50 (including asthma and chronic obstructive pulmonary disease [COPD]), and acute heart failure (HF)
51 events resulting in respiratory symptoms (e.g. breathlessness). Before the COVID-19 pandemic,
52 European healthcare costs for pneumonia alone in adults were estimated at €10 billion annually,
53 including €5.7 billion for inpatient care. [1] Pneumonia incidence in Europe varies by country and intra-
54 country region, age, socioeconomic status, and gender; [2-4] however, in all studies pneumonia
55 incidence in adults increases sharply with age. [3] Pneumonia affects an estimated 0.5% to 1% of UK
56 adults each year [5, 6]. Overall LRTI incidence is considerably higher with ~15% of UK adults aged ≥65
57 years experiencing an event each year.[7] Whilst HF is not typically clinically included as an acute
58 respiratory illness, HF with respiratory symptoms may be caused by respiratory viral infection, such as
59 respiratory syncytial virus (RSV), either acutely or 3-4 weeks after the primary infection [8, 9].

60
61 However, aLRTD incidence may be considerably higher than previously reported, given that published
62 literature has documented several reasons why previous estimates may have been erroneously low
63 [1]. Estimates of aLRTD based on pneumonia defined as radiologically demonstrated alveolar
64 infiltrates, may underestimate true disease burden as chest radiography (CXR) is an imperfect gold-
65 standard. [10, 11] Immunosuppressed, elderly or dehydrated patients are likely to be under-
66 represented if respiratory infection is defined by radiologically demonstrated changes. [10, 11]
67 Microbiological investigations for pneumonia are undertaken variably and identify a causative
68 pathogen in 50% of cases at most [12, 13]; hence, the disease is probably under-reported when
69 confirmed microbiological diagnosis is required. Furthermore, Respiratory Syncytial Virus (RSV)
70 infection has recently been recognized as an important respiratory pathogen later in life, [9] with
71 severe disease occurring in patient groups in whom the diagnosis is likely to be under-recognized (e.g.

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3 72 the elderly or those with underlying cardiac conditions). [8] Studies of clinical coding data are
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5 73 retrospective and subject to recognized limitations associated with this methodology [14, 15]. Older
6
7 74 patients with pneumonia often have atypical presenting signs and symptoms, which may lead to
8
9 75 missed or incorrect admission diagnoses. [16] Pneumonia may occur secondary to, or be an underlying
10
11 76 cause of, the main presenting complaint, particularly in patients with cerebrovascular accidents (CVA),
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14 77 HF, COPD exacerbations or altered consciousness levels. [17] In these scenarios, pneumonia may not
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16 78 be the primary hospitalization diagnosis code and may not even be coded as an associated diagnosis.
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22 80 There are many studies examining the incidence of acute respiratory illness in children; however, data
23
24 81 on respiratory illness in adults in the UK is lacking. Given the paucity of data supporting accurate aLRTD
25
26 82 incidence rates and its disease subsets in adults, we undertook to assess aLRTD incidence by two
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28 83 approaches (retrospective and prospective) in Bristol, UK, seeking to determine the disease burden of
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30 84 hospitalized aLRTD and its subgroups more accurately.
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86 **Methods**

87 *Study Design*

88 This study was conducted at a large secondary care institution in UK (North Bristol NHS Trust) with
89 specialist Respiratory Services (interstitial lung disease, pleural disease). Two approaches were
90 undertaken to estimate aLRTD incidence: (1) “retrospective analysis” of aLRTD International
91 Classification of Diseases Tenth Revision (ICD-10) diagnostic codes for an entire year; and, (2) 21-day
92 observational “prospective review” of aLRTD hospital admissions.

93 *Ethics*

94 This study was approved by North Bristol NHS Trust Research Audit Ethics Committee (CA52218).

95 *Patient and Public Involvement*

96 No patient involved.

97 *Retrospective Analysis*

98 For the retrospective analysis, all adult inpatient admissions (≥ 18 years) obtained from Hospital
99 Episode Statistic (HES) to the study hospital during March 2018–February 2019 with aLRTD ICD-10
100 diagnostic codes (Supplementary data 1) in any of the first 5 positions were identified and categorized
101 into aLRTD subgroups: pneumonia, NP-LRTI, other LRTD, and HF (Supplementary data 2). A mutually
102 exclusive hierarchy was used (pneumonia, NP-LRTI, then other LRTD) although HF diagnoses could co-
103 occur with other categories. “Other LRTD” included acute respiratory events that could not definitively
104 be placed in another category. Only the first 5 ICD-10 codes were available for analysis.

105 *Prospective Review*

106 Adult patients (≥ 18 years) resident within Bristol, North Somerset, and South Gloucestershire Clinical
107 Commissioning Group (CCG) referred to the Acute Medical Unit (AMU) at North Bristol NHS Trust
108 during 19th August –9th September 2019 were included in an audit on acute respiratory illness. This

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3 109 time period was selected because it was felt to represent a period when there were an average
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5 110 number of adults hospitalised with aLRTD. A respiratory physician (CH) reviewed presenting features
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7 111 and investigation results for each admitted patient to determine whether aLRTD was present. Further
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10 112 medical record review was undertaken if patients had: new/worsening breathlessness, cough or
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12 113 sputum production; new or worsening peripheral oedema; pleurisy; clinical examination findings
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14 114 consistent with respiratory infection or HF; or fever attributable to suspected respiratory infection.
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16 115 Patients with non-respiratory diagnoses were excluded. There were no patient refusals for either
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18
19 116 approach.

21 117 *Prospective Review Outcome measures*

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24 118 aLRTD was considered confirmed in individuals with: new/worsening respiratory symptoms, with or
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27 119 without fever; sepsis, delirium or raised inflammatory markers attributable to likely respiratory
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29 120 infection in admitting clinical team's opinion; radiological change in keeping with infection (e.g.
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31 121 consolidation); and/or final diagnosis of NP-LRTI, pneumonia or infective exacerbation of a chronic
32
33 122 respiratory condition. A pneumonia diagnosis was assigned if radiological changes likely due to
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36 123 infection were described by the reporting radiologist. An NP-LRTI diagnosis was assigned if aLRTD signs
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38 124 and symptoms likely to be due to infection were present without demonstrated radiological change.
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40 125 A HF diagnosis was assigned in presence of: new/worsening breathlessness and bi-basal crepitations,
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42 126 cardiac wheeze or new/worsening bilateral pitting oedema; elevated pro-NT BNP (≥ 450 pg/mL);
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44 127 radiologist-reported radiographic changes consistent with cardiac failure; or a final consultant
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47 128 physician diagnosis of HF, cardiac failure or left-ventricular failure. When present, ≥ 1 diagnosis was
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49 129 selected.

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52 130 For both retrospective and prospective studies, pneumonia included both community and healthcare
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54 131 setting acquired cases; although, the prospective review only captured admitting diagnoses and
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56 132 pneumonias occurring later during hospitalization were not included.

59 133 *Incidence calculations*

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3 134 Annual incidence per 100000 persons was calculated for both retrospective and prospective studies.
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5 135 Case counts from prospective review were annualized (i.e., case counts by diagnosis and overall were
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7 136 divided by the percentage of annual admissions for these diagnosis groups that occurred in this 21-
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9
10 137 day period in the retrospective analysis).

138 *Incidence Denominators*

139 To calculate appropriate population denominators for incidence calculations, aLRTD hospital
140 admission event data were linked to aggregated GP practice patient registration data within the NHS
141 Bristol, North Somerset, and South Gloucestershire CCG for 2017–2019. Only 4% of patients sought
142 care at North Bristol NHS Trust hospital from outside these local CCGs, despite presence of specialist
143 respiratory services. In the UK, GP registration is available free of charge for all, regardless of
144 residential status. For GP practices within these same CCGs, the proportion of their aLRTD admissions
145 occurring at North Bristol NHS Trust was multiplied by their patient registration count in 2019 by age
146 group, to get each practice's contribution to the denominator (e.g. if 50% aLRTD admissions were at
147 North Bristol among persons 50–64 years, the practice would contribute half of their patients 50–64
148 years to the denominator). Further details of this methodology have been described previously. [18]

149

150 *Statistical analysis*

151 Patient characteristics were tabulated by aLRTD diagnosis. Categorical variables were presented as
152 counts with percentages. Continuous data are presented with means and standard deviations (SD) if
153 normally distributed and medians and interquartile range (IQR) if not normally distributed. Patient
154 groups difference were evaluated using the Friedman test with Wilcoxon signed-rank test.

156 **Results**

157 *Retrospective analysis*

158 Over a 12-month period, we identified 7727 hospital admissions for aLRTD: 3005 NP-LRTI admissions,
159 2402 pneumonia, 1633 HF and 1071 other LRTD (Table 1). aLRTD admissions were lowest in March
160 and April and highest December through February (Figure 1A), overall and for all aLRTD subgroups
161 ($P<0.05$) (Figure 1B-D). Overall, 28.1% (2244) cases were identified as being potentially hospital-
162 acquired infection based on co-occurring ICD-10 code 'Y95 Nosocomial Infection'.

164 *Prospective review*

165 Among 1322 eligible adult patients referred to AMU over the 21-day review period (Figure 2), 410
166 patients had signs or symptoms of aLRTD: 188 (46%) NP-LRTI; 152 (37%) pneumonia, and 77 (19%) HF.
167 Seven patients had both decompensated HF and a respiratory infection at hospital admission. On
168 admission, >10% of aLRTD patients did not have respiratory symptoms: 16 (11%) pneumonia, 25 (13%)
169 NP-LRTI, and 18 (14%) HF (Table 2).

170 Almost all adults admitted with aLRTD underwent routine biochemistry, hematology, and radiological
171 investigation (99.9%, $n=409$). In contrast, only 150 (37%) patients with aLRTD had microbiological
172 testing performed: blood cultures ($n=149$, 36%) and urine cultures ($n=143$, 35%). Pneumonia patients
173 more commonly underwent microbiological investigation than NP-LRTI patients ($P<0.05$) with highest
174 disparity in rates of sputum culture, urinary antigens, and respiratory viral PCR (Table 2). All cardiac
175 failure patients who underwent microbiological investigation had concomitant respiratory infection
176 (Table 2). Overall, a microbiological diagnosis was found in 11 (3%) cases, highlighting the low
177 frequency of definitive pathogen identification in aLRTD. Younger patients underwent microbiological
178 testing more frequently than the elderly for all aLRTD categories (Table 2).

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3 180 *Disease incidence*
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6 181 Retrospective analysis yielded an overall aLRTD incidence of 1901 per 100000. Disease incidence rose
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8 182 with increasing age (Table 3), both overall and for all disease subgroups; incidences per 100000 among
9
10 183 adults aged ≥ 85 years were: 11430 (aLRTD), 6116 (NP-LRTI), 4215 (pneumonia) and 4005 (HF). Overall,
11
12 184 28.1% aLRTD hospitalizations also included an ICD-10 discharge code for 'nosocomial infection',
13
14 185 suggesting the aLRTD event or other infection was hospital-acquired. For pneumonia 25.3% had the
15
16 186 nosocomial infection code. If all of these were related to the pneumonia diagnosis, an estimated
17
18 187 residual 1794 events would have been community-acquired pneumonia (annual incidence
19
20 188 441/100000 adults). Among older age categories, where the incidence of aLRTD was highest, NP-LRTI
21
22 189 incidence was similar to pneumonia incidence, with an approximate 1:1 ratio of NP-LRTI to pneumonia
23
24 190 cases. However, among adults under age 50 years, there were approximately twice as many NP-LRTI
25
26 191 cases observed as pneumonia cases. Incidence calculations using annualized prospective review
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28 192 results were broadly comparable with retrospective analysis of ICD-10 data (Table 3).
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Discussion:

This is the first UK study to assess aLRTD incidence comprehensively. We conducted an analysis of 12-months of hospital admissions by ICD-10 diagnosis code data and a 21-day prospective review at a large academic hospital in southwest England. With both approaches, we found a high annual incidence of aLRTD (>1700 per 100000; 1.7%), pneumonia (~0.6%), NP-LRTI without pneumonia (>0.7%), and HF (>0.4%). Incidences increased sharply in a non-linear manner as age increased above 65 years for all aLRTD categories. These results suggest rates are probably significantly higher than previous disease estimates from the UK (Table 4) but comparable with many results globally, [19, 20] with important consequences for healthcare resources. For example, a recent review highlighted that pneumonia incidences ranged from 1000 to 2500 per 100000 (1–2.5%) among persons aged 65–74 years in Spain, Germany, France, Japan and the US, which are comparable to the >1250 per 100000 (1.3%) reported here. Some of the potential sources of underestimation for other UK incidence studies (Table 4) include: case source and denominator mismatch; use of first position in ICD-code analysis only; inclusion of enrolled subjects in consent-based prospective studies only; requiring specific symptoms and chest x-ray confirmation in order to be classified as pneumonia/aLRTD; and, lastly, the rising incidence of aLRTD.

Comparison with published literature

No studies have reported aLRTD incidence comprehensively in UK hospitalized patients within the last 20 years. However, eight publications report incidence of ≥ 1 aLRTD subgroup. Seven publications reported community-acquired pneumonia (CAP) incidence (three from Nottingham, UK). For pneumonia, our incidence estimates were three to four-fold higher than other UK inpatient incidence estimates (Table 4) but comparable to estimates from other countries. [19, 20] Only two UK studies from approximately 20 years ago reported NP-LRTI incidence (one with both CAP and NP-LRTIs; Table 4), and only one provided an inpatient estimate. [21] NP-LRTI incidence was approximately 2-fold

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3 218 lower than that calculated here, taking into account inclusion of CAP and other NP-LRTI in their
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5 219 estimates. [21, 22] The one UK study reporting HF incidence had methodological differences (i.e.,
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7 220 inclusion of outpatients and limiting to initial HF diagnosis) and estimates could not be compared. [23]
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9 221 Close examination of the existing literature methods yielded multiple sources for potential
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11 222 underestimation.
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15 223 First, for incidence studies that were not countrywide, identifying an appropriate denominator is
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17 224 challenging. Like many other inpatient settings worldwide, UK hospitals' catchment areas for acute
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19 225 treatment are principally driven by geography, but the proportion of any area's residents expected to
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21 226 use the hospital becomes less clear as distance from the hospital increases because catchment areas
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23 227 and populations of different hospitals may overlap. Defining hospital catchment populations based
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25 228 solely on census data cannot account for this variability. Including all geographic areas using the
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27 229 hospital to any extent results in population denominator overestimation and underestimated
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29 230 incidence. Here, we addressed this by calculating population denominators based on hospital
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31 231 utilization behavior from referring General Practices.
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36 232 Second, other studies used fewer codes in their ICD code analysis: all limited their analyses to events
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38 233 where the diagnostic code was in the first position (Table 4; case definition column), potentially
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40 234 excluding admissions in which pneumonia/NP-LRTI complicated other underlying respiratory diseases,
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42 235 including COPD and asthma. Limiting to first position has been shown to reduce sensitivity for
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44 236 pneumonia events by about 30% (66%–72% sensitive). [22, 24] Conversely, the recent British Thoracic
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46 237 Society (BTS) audit on CAP found ~27% of pneumonia events identified by ICD code (J12-18) had no
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48 238 new CXR infiltrates. [6] Even accounting for this potential over coding practice, our estimates remain
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50 239 well above other published UK estimates.
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54 240 Third, for other prospective studies, exclusion of events where patients did not consent to
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56 241 participation or were not identified by study surveillance processes (often conducted predominately
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58 242 during business hours) can introduce underestimation. Further, other prospective pneumonia studies
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3 243 specifically required documentation of specific symptoms, radiological findings, and treatments, [25]
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5 244 potentially excluding those without these features documented in medical records. In our prospective
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7 245 review, approximately 11% did not display typical signs and symptoms of pneumonia and could have
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9 246 been excluded by that requirement. Requiring CXR confirmation has been shown to reduce incidence
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11 247 estimates for pneumonia, [20] although all pneumonia events in our prospective review were
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13 248 radiologically confirmed.

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17 249 Fourth, trends over time may also contribute to our estimates being higher than previous reports. Our
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19 250 study's estimates are recent, and rising incidence of pneumonia has been documented in all studies
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21 251 that have reported such trends. [25-27]

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24 252 Finally, this study included, in part, hospital-acquired pneumonias (HAP), which were excluded from
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26 253 estimates calculated in some other studies (Table 4). The retrospective analysis may have included
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28 254 more nosocomial infection than the prospective review, as the latter was focused on evaluation of
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30 255 patients at admission for aLRTD and would not have reliably captured events that developed during
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32 256 hospitalization. 25.3% pneumonia events included a nosocomial infection code, but this code could
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34 257 relate to any nosocomial infection during that hospitalization. If all these cases were assumed to be
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36 258 hospital-acquired pneumonia, our estimates community-acquired pneumonia incidence would still be
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38 259 well above prior UK estimates: 441/100000 (≥ 18 years).

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43 260 While not impacting all-cause aLRTD incidence estimates discussed above, during the prospective
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45 261 review, we found low rates of microbial investigation which prevented us from generating pathogen-
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47 262 specific incidence estimates. Only 52% of patients with radiologically-confirmed pneumonia
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49 263 underwent microbiological testing during hospitalization, with even lower rates in other aLRTD
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51 264 subgroups (41% NP-LRTI and 14% HF). Microbiological testing occurred less frequently as age
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53 265 increased, particularly in NP-LRTI patients. It is possible that, because aLRTD hospitalizations are
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55 266 substantially more common among older persons, less etiologic investigation is performed.
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57 267 Furthermore, clinicians may elect to treat elderly patients with a more pragmatic and less invasive
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3 268 approach. Management guidelines do not require specific pathogen identification to inform treatment
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5 269 choice. Presence only of atypical features on presentation (in this series, 13% NP-LRTI and 11%
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7 270 pneumonia cases) may also reduce the likelihood of timely microbiological testing. Low rates of
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9 271 microbiological testing, and consequently of confirmed microbiological diagnosis, may represent a
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11 272 source of underestimation of pathogen-specific disease incidence in patient groups (i.e., testing bias),
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13 273 particularly in elderly patient groups.
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20 275 *Strengths and Limitations of This Study*

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23 276 This study has many strengths. First, this study used two analytical methods at the same site over a
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25 277 comparable period, to calculate incidence using both prospective and retrospective approaches.
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27 278 Second, the case burden of aLRTD and its subgroups was pre-defined and included patients with
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29 279 atypical presentations but with clinical and/or radiological diagnoses, who may otherwise have been
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31 280 excluded from analysis. Additionally, we calculated incidence using a denominator derived from GP
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33 281 records, providing increased accuracy compared to population calculations based on census data.
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36 282 However, the study also had some limitations. This was a single-center study, with a predominantly
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38 283 Caucasian cohort; therefore, the findings might not be generalizable to other populations both within
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40 284 the UK and in other countries. Different healthcare systems may affect patient treatment preference,
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42 285 and as the NHS provides care which is free at the point of access, the hospitalization rates seen in this
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44 286 study may be different in fee or insurance based healthcare system. Similarly, physician treatment
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46 287 preferences may affect hospitalization rates, and we have not explored these in this analysis. The ICD-
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48 288 10 coding data analysis was limited to codes within the first five positions, and therefore may have
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50 289 excluded some cases where other diagnoses were placed higher in the diagnostic coding hierarchy.
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52 290 Furthermore, we could not determine how many cases of the 28.1% ICD-10 cases also coded with
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54 291 nosocomial infection had hospital-acquired respiratory infection rather than other nosocomial
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56 292 infections.
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3 293 Although the denominator used to calculate incidence was derived from GP records, this was still an
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5 294 estimate as there is no precisely defined denominator hospital catchment. We were unable to exclude
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7 295 patients from outside the local CCGs in the retrospective analysis, due to the way ICD-10 data was
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9 296 obtained. However, these patients were excluded from the prospective review and the incidence
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11 297 calculated was comparable, suggesting any effect that patients attending North Bristol NHS Trust from
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13 298 outside the local CCGs have on incidence estimates is minimal. This may be because any effect of
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15 299 travelling or health-seeking behavior is bi-directional: whilst some patients admitted to Southmead
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17 300 hospital were from outside the local area, it is also true that patients with aLRTD within the relevant
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19 301 CCGs would have been admitted to other hospitals. We also acknowledge the 21-day prospective
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21 302 review period was relatively short, not repeated and may not be fully representative of clinical practice
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23 303 and cases throughout the year. This study was conducted before the emergence of COVID-19, and we
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25 304 think these data will be useful in one of two ways in the context of COVID-19: (1) either COVID-19 will
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27 305 become endemic, and the data will reflect the first year before a new normal, or (2) COVID-19 will
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29 306 abate and it will provide an anchor for understanding incidence during a respiratory viral pandemic'
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38 308 In conclusion, we found similarly high estimates of LRTD incidence using two different approaches,
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40 309 and these estimates were higher than those obtained previously in the UK. Determining if there is a
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42 310 real increase in incidence, or if this estimate is larger due to more accurate methodology including a
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44 311 more accurate denominator will require ongoing comprehensive surveillance. Nonetheless,
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46 312 combining all types of LRTD highlights the high burden for this important and potentially life-
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48 313 threatening disease group. Incidence assessments require close assessments of potential areas of
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50 314 under ascertainment, including unidentified or unenrolled cases in prospective studies, reduced
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52 315 positions or number of ICD-10 codes included for retrospective studies, and population denominator
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54 316 mismatch for all study types. Our prospective review findings highlight the need to consider atypical
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56 317 clinical presentations for pneumonia and the lack of routine microbiological investigation in many
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3 318 aLRTD patients required for pathogen-specific aLRTD incidence calculation. Future research should
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5 319 include a fully prospective assessment of aLRTD incidence with comprehensive diagnostic testing
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7 320 across multiple respiratory seasons, to ensure accurate capture of all aLRTD events, particularly in the
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9 321 elderly. Such research should be undertaken given the high and rising aLRTD burden to enable
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11 322 appropriate healthcare planning and identification of interventions which may reduce disease burden.
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13 329 Harvey Walsh Limited.
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18 331 **Data Sharing**
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20 332 No additional data available
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Table 1: Demographic Characteristics of Patients admitted with aLRTD for 1 Year ICD-10 code Retrospective Analysis and 21-day Prospective Review**Period -- 2018–2019**

Characteristic	Pneumonia		NP-LRTI		Heart Failure		Other LRTD	All LRTD	
	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Retrospective Review Only	Prospective review	Retrospective analysis
N	152	2402	188	3005	77	1633	1071	410	7727
Gender, females	61 (40)	1078 (45)	99 (53)	1482 (49)	39 (51)	731 (45)	489 (46)	194 (47)	3780 (49)
Age									
Median (IQR), y	80 (67-86)	81 (66-88)	70 (46-87)	69 (45-87)	87 (72-90)	87 (70-90)	74 (53-82)	80 (64-88)	81 (65-90)
18-24	4 (3)	72 (3)	9 (5)	151 (5)	0 (0)	0 (0)	26 (2)	13 (3)	249 (3)
25-34	2 (2)	48 (2)	12 (6)	183 (6)	0 (0)	3 (0)	33 (3)	14 (3)	267 (3)
35-44	6 (4)	97 (4)	14 (7)	209 (7)	2 (3)	10 (1)	59 (6)	22 (5)	375 (5)
45-54	8 (5)	118 (5)	11 (6)	183 (6)	0 (0)	22 (1)	112 (10)	19 (5)	435 (6)
55-64	18 (12)	293 (12)	19 (10)	305 (10)	8 (10)	158 (10)	210 (20)	45 (11)	966 (13)
65-74	34 (22)	501 (21)	32 (17)	549 (18)	10 (15)	199 (12)	223 (21)	75 (18)	1472 (19)
75-84	44 (28)	667 (28)	40 (21)	621 (21)	20 (30)	498 (31)	205 (19)	100 (24)	1991 (26)
≥85	38 (26)	606 (25)	51 (27)	704 (23)	37 (55)	742 (45)	203 (19)	123 (30)	2255 (29)

Table 2. Clinical Characteristics and Investigations of Patients admitted with aLRTD over 21-day Prospective Review Period in August-September 2020

Characteristic	Pneumonia n=152 (%)	NP-LRTI n=188 (%)	Heart Failure n=77 (%)	All LRTD n=410 (%)
GP	56 (37)	72 (39)	30 (39)	158 (39)
A&E department	93 (61)	100 (54)	45 (58)	238 (58)
Transfer from another unit	2 (1)	13 (7)	0 (0)	15 (4)
Other	1 (1)	1 (1)	2 (3)	4 (1)
Referral Source				
Typical features†	136 (89)	163 (87)	63 (82)	355 (87)
Atypical features	16 (11)	25 (13)	14 (18)	55 (13)
- collapse/falls	11 (7)	12 (6)	0 (0)	23 (6)
- confusion	0 (0)	7 (4)	4 (5)	10 (2)
- drowsiness	1 (1)	1 (1)	2 (3)	4 (1)
- off legs/generally unwell	5 (3)	5 (3)	8 (10)	18 (4)
LRTD Signs and symptoms on referral to AMU				
Biochemistry	152 (100)	185 (99)	77 (100)	419 (100)
Haematology	152 (100)	185 (99)	77 (100)	419 (100)
Radiology	152 (100)	185 (99)	77 (100)	419 (100)
Investigations Performed				
<i>Testing by Age Group</i>				
All patients	79/152 (52)*	77/188 (41)	11/77 (14)	167 (41)
18-24	3/4 (75)	6/9 (66)	0/0 (0)	9/13 (69)
25-34	0/0 (0)	6/12 (50)	0/0 (0)	6/12 (50)
35-44	5/6 (83)	10/14 (71)	2/2 (100)	17/22 (77)
45-54	6/8 (75)	6/11 (55)	0/0 (0)	13/19 (68)
55-64	11/18 (61)	12/19 (63)	5/8 (63)	31/45 (69)
65-74	15/34 (44)	12/32 (38)	1/10 (10)	28/75 (37)
75-84	21/43 (49)	10/40 (25)	2/20 (10)	33/100 (33)
≥85	18/39 (46)	15/51 (19)	1/37 (3)	34/124 (27)
Test performed				
Blood culture	79 (52)	70 (37)	5 (6)	150 (37)
Urine culture	66 (43)	77 (41)	11 (14)	150 (37)
Sputum culture	27 (18)*	7 (4)	2 (3)	35 (9)
BinaxNOW® Pn UAT ‡	29 (19)*	6 (3)	0 (0)	35 (9)
Respiratory virus PCR	16 (11)*	11 (6)	1 (1)	28 (7)
Pleural fluid culture	3 (2)	0 (0)	1 (1)	4 (1)

A&E, Accident and Emergency department; GP, general practitioner; LRTD, lower respiratory tract disease; NP-LRTI, non-pneumonic lower respiratory tract infection; IQR, interquartile range; Pn UAT, pneumococcal urinary antigen test; PCR, polymerase chain reaction.

* $P < 0.05$.

† Typical symptoms included cough, breathlessness, increased or discolored sputum production, wheeze, pleurisy, peripheral oedema, haemoptysis, reduced exercise tolerance and/or fever.

‡ BinaxNOW Pn UAT was only performed in accordance with NICE/BTS guidelines.

Table 3: Incidence of aLRTD resulting in hospital admission based on prospective and retrospective approaches by age group and condition, North Bristol National Health Service Trust— United Kingdom 2018–2019.

	Age Groups					
	All Adults	18-49 y	50-64 y	65-74 y	75-84 y	≥85 y
Population in 2018	406481	226920	91534	45705	29487	12835
Retrospective Analysis of a Year's ICD-10 codes						
Annual cases – N (row %)						
All aLRTD	7,727	1,130 (14)	1,103 (14)	1,684 (22)	2,053 (27)	1,757 (23)
Pneumonia	2,402	264 (11)	288 (12)	589 (25)	720 (30)	541 (22)
NP-LRTI	3,005	576 (19)	410 (14)	572 (19)	662 (22)	785 (26)
Other LRTD	1,071	246 (23)	268 (25)	226 (21)	200 (19)	131 (12)
Heart Failure	1,633	48 (3)	189 (12)	397 (24)	485 (30)	514 (31)
LRTI/Pneumonia Ratio	1.3	2.2	1.4	1.0	0.9	1.5
Incidence (per 100,000)						
All aLRTD	1,901	497	1,205	3,684	6,962	13,689
Pneumonia	591	116	315	1,289	2,442	4,215
NP-LRTI	739	254	448	1,252	2,245	6,116
Other LRTD	263	108	293	494	678	1,021
Heart Failure	402	21	206	869	1,645	4,005
21-day Prospective Review (annualized)						
Annualized cases – N (row %)						
All aLRTD	7,885	1,038	962	1,692	2,231	1,962
Pneumonia	2,621	224	397	776	690	534
NP-LRTI	3,857	796	531	653	1,061	816
Heart Failure	2,000	51	205	308	641	795
LRTI/Pneumonia Ratio	1.5	3.6	1.3	0.8	1.5	1.5
Incidence (per 100,000)						
All aLRTD	1,940	458	1,050	3,703	7,565	15,283
Pneumonia	645	99	433	1,698	2,339	4,164
NP-LRTI	944	351	580	1,429	3,599	6,360
Heart Failure	492	23	224	673	2,174	6,193

LRTI = lower respiratory tract infection; LRTD = lower respiratory tract disease.

Pneumonia category includes community and healthcare acquired. For retrospective ICD-10 based cohort, the following mutually exclusive hierarchy was used to define pneumonia, LRTI, and other LRTD; heart failure event could overlap with other categories.

“Other LRTD” contains LRTD events that could not definitively be placed in one of the other respiratory disease categories.

Table 4: Literature review of aLRTD incidence in hospitalized adults, United Kingdom

Study	Study Years	Location (Facility)	Event Setting	Age	Case Definition ^b	Key inclusion	Denominator Source	Overall Incidence	Age Breakdown (years)	Incidence per 100,000 by age ^d	Comments
Community –acquired Pneumonia											
Current Study	2018 – 2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms with radiological change in keeping with infection (prospective review portion) AND Retrospective ICD-10 code analysis (1 st 5 positions): J12-J18, J85, and J86	Hospital-acquired pneumonia (HAP) included	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	648	18 –49	116	Retrospective analysis includes 1 st 5 positions
									50 –64	315	
								591	65 –74	1,289	
									75 –84	2,442	
								≥85	4,215		
Elston 2012, Epidemiol Infect	2002 – 2009	Hull and East Yorkshire Hospitals ^c	Inpatients only	≥16 y	ICD-10 codes (1 st position only): J18.0, J18.9, J13X, J18.1, and J15X	HAP included	Mid-year population estimates for Hull (city) and EroY (Surrounding County) from Office for National Statistics	143 (2002) – 207 (2009)	15 –64	48.8 – 84.1	Fewer ICD-10 codes included than other analyses; Y95 Nosocomial infection included.
								≥65	543 – 781		
Millet 2013, J Clin Epidemiol	1997 – 2011	UK	Both inpatients and outpatients	≥65 y	Read and ICD 10 codes; no specified codes provided. For ICD-10, used first diagnosis code for first episode of hospitalization only.	HAP Excluded	Mid-year UK population estimates from Office for National Statistics	799	65 –69	281	Incidence estimates converted to per 100,000 person-years
									70 –74	431	
									75 –79	694	
									80 –84 y	1,205	
									85 –89	2,184	
								≥90	4,194		
Pick 2020, Thorax ^a	2013 – 2014	Nottingham (2 large university hospitals)	Inpatients only	≥16 y	Inclusion criteria: one or more symptom suggestive of LRTI (defined as cough, increasing dyspnea, sputum production and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP Exclusion criteria: hospitalization within 10 days of index admission, a diagnosis of tuberculosis or post-obstructive pneumonia.	HAP Excluded	Mid-year estimates for the Greater Nottingham area from the Office for National Statistics, including local population data stratified by age group	96.3	16 –49	27.3	Only consented/enrolled subjects included in estimates Required CXR - confirmation but not all LRTI patients had CXR Census-derived denominator that may not have fully matched catchment area.
									50 –64	80.2	
									65 –74	181.3	
									75 –84	400.6	
									≥85	707.5	
	2017 – 2018							158.4	16 –49	29.9	
									50 –64	146.9	

								120.4	65–74 75–84 ≥85	310.4 559.5 1522.6	Required specific symptoms and evidence of treatment and some CAP events may not have had this information documented	
	2013–2018							--	--	--		
Thorrington 2019, BMC Med	2004–2005 2014–2015	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J18 (pneumonia of unspecified causative organism)	HAP Included	Mid-year population estimates for England for 2004 to 2015 from Office for National Statistics	NA	≥65	829	Incidence is per 100,000 person-years. Fewer ICD-10 codes included than other analyses	
									≥65	1787		
Trotter 2008, EID	1997–1998	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J12–J18	HAP Included	Mid-year population estimates for England for 1997 to 2004 from the Office for National Statistics	NA	65–74 75–84 ≥85	263 684 1599	Incidence estimates converted to 100,000 population	
	2004–2005								65–74 75–84 ≥85	355 877 2218		
Lower Respiratory Tract Infection												
Pneumonia												
Current Study	2018–2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change AND Retrospective ICD-10 code analysis: J09, J10, J11; J20, J21, J22, J40, J41, J42, J44, J45, and J46	Excludes all Pneumonia	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	802	18–49 50–64 65–74	254 448 1,252		
								739	75–84 ≥85	2,442 6,116		
Lovering 2001, Clinical Micro. & Infection	1994–1996	Bristol (Southmead Hospital)	Inpatients only	≥16 y	LRTI episodes from four groups by ICD 9/10 codes: (1) CAP; (2) chest infection or acute exacerbation in presence of asthma; (3) chest infection or acute exacerbation in presence of COPD; or (4) bronchitis with no radiological evidence of pneumonia or pre-existing respiratory disease, such as COPD or asthma. No specified codes provided.	Includes Community-acquired Pneumonia HAP Excluded	No information on denominator provided	623	16–39 40–49 50–59 60–69 70–79 >79	151 175 294 1,086 2,135 3,141	Incidence converted to per 100,000 population Study involved single hospital and no mention of source of denominator mentioned.	
Millet	1997–	UK	Both	≥65 y	Read and ICD 10 codes; no specified	Includes	Mid-year UK population	12,293	65–69	9,221	Incidence	

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2013, J Clin Epidemiol	2011	inpatients and outpatients	codes provided. For ICD-10, used first diagnosis code for inpatient episode only.	Community-acquired Pneumonia	estimates from Office for National Statistics. (Patients were not considered at risk for community-acquired LRTI during an LRTI illness-episode, during a HES hospitalization, or for 14 days after any HES hospitalization or CPRD hospital code. This person-time was excluded from denominator.)	70–74 75–79 80–84 85–89 ≥90	10,740 12,607 15,137 18,791 26,287	converted to per 100,000 person years
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Heart Failure										All or First Episode		
Current Study	2018-2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change	All	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	328	18–49 50–64 65–74 75–84 ≥85	21 206 869 1,645 4,005		
					AND Retrospective ICD-10 code analysis: I110; I130; I132; I50			402				
Uijl 2019, Eur J Heart Fail	2000–2010	UK	Both inpatients and outpatients	≥55 y	4 sources of HER were linked: CPRD primary care records, HES secondary care hospital charges, Myocardial Ischaemia National Audit Project (MINAP) disease registry, and ONS national death registry. HES ICD-10 codes: Heart failure: I110, I130, I132, I260, I50 and I21. Individuals were excluded if they presented a history of HF before their index date in CPRD, HES or MINAP.	First episode at 55 years or older counted	Not Reported	Not Reported	55–64, M 55–64, F 65–74, M 65–74, F >75, M >75, F	360 190 1,360 920 3,440 2,800	Incidence converted to per 100,000 person years Included first episode of HF (inpatient or outpatient) at age 55 and up, so repeat episodes not included.	

^a Only the most recent incidence estimates from the Nottingham CAP study were included.

^b Add text names for all listed ICD codes in this footnote or appendix.

^c Included hospitals were Hull Royal Infirmary, Castle Hill Hospital, Princess Royal Hospital, Scarborough District General Hospital, Bridlington & District Hospital, York Teaching Hospital, Scunthorpe General Hospital, Goole & District Hospital.

^d For the current study, only age-group estimates from the retrospective analysis were included in this table, but these were closely comparable to the annualized incidence estimates based on the prospective review. See Table 3 for full results.

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3 **Figure Legends:**
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5 **Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North**
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7 **Bristol National Health Service Trust— United Kingdom 2018–2019.**
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10 Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower
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12 Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Non-pneumonic
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14 Lower Respiratory Tract Infection (NP-LRTI) (white bars), (D) Other LRTD (cross-hash bars), and (E)
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16 Heart Failure (grey bars).
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21 **Figure 2: Flow diagram of the Prospective Review**
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For peer review only

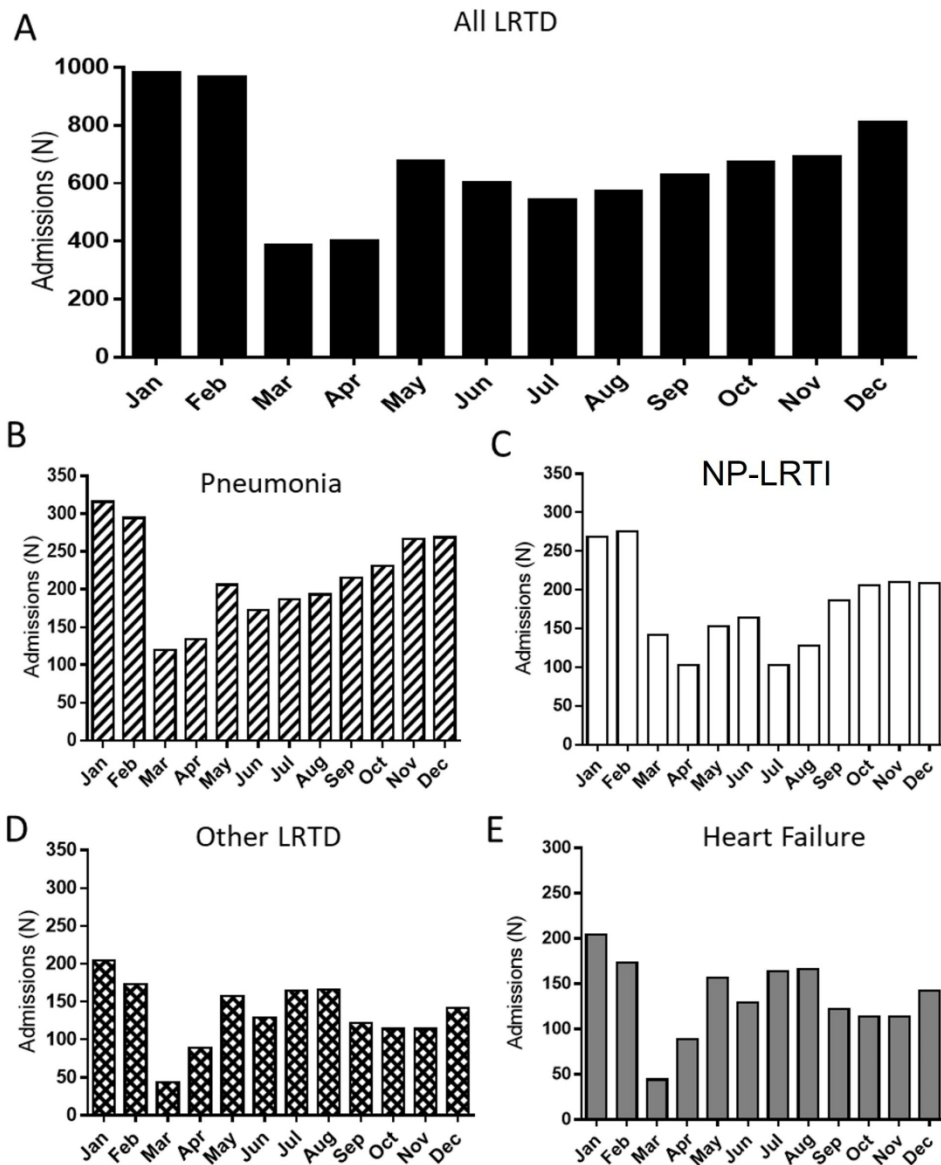


Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North Bristol National Health Service Trust— United Kingdom 2018–2019. Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Non-pneumonic Lower Respiratory Tract Infection (NP-LRTI) (white bars), (D) Other LRTD (cross-hatch bars), and (E) Heart Failure (grey bars).

169x207mm (300 x 300 DPI)

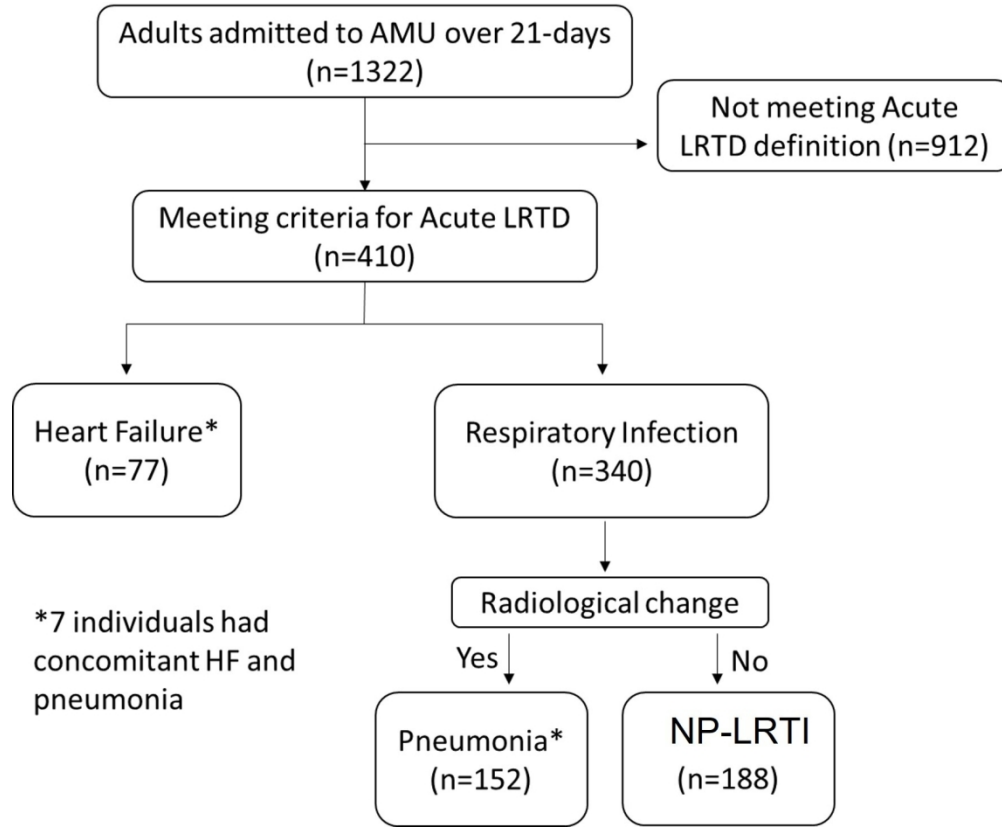


Figure 2: Flow diagram of the Prospective Review

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Supplementary Data 1: ICD-10 codes used for patient identification for Retrospective Analysis

ICD-10 code	Definition	Pneumonia	NP-LRTI	HF	Other aLRTD
J09	Influenza due to identified zoonotic or pandemic influenza virus		X		
J10	Influenza due to identified seasonal influenza virus		X		
J11	Influenza, virus not identified		X		
J12	Viral pneumonia, not elsewhere classified	X			
J13	Pneumonia due to <i>Streptococcus pneumoniae</i>	X			
J14	Pneumonia due to <i>Haemophilus influenzae</i>	X			
J15	Bacterial pneumonia, not elsewhere classified	X			
J16	Pneumonia due to other infectious organisms, not elsewhere classified	X			
J17	Pneumonia in diseases classified elsewhere	X			
J18	Pneumonia, organism unspecified	X			
J20	Acute bronchitis		X		
J21	Acute bronchiolitis		X		
J22	Unspecified acute lower respiratory infection		X		
J40	Bronchitis, not specified as acute or chronic		X		
J41	Simple and mucopurulent chronic bronchitis		X		
J42	Unspecified chronic bronchitis		X		
J43	Emphysema				X
J44	Other chronic obstructive pulmonary disease (including J44.0 chronic		J44.0 only		X (J44.0)

	obstructive pulmonary disease with acute lower respiratory infection)				
J45	Asthma				X
J46	Status asthmaticus				X
J47	Bronchiectasis				X
J85	Abscess of lung and mediastinum		X		
J86	Pyothorax		X		
J90	Pleural effusion, not elsewhere classified				X
J91	Pleural effusion in conditions classified elsewhere				X
J95	Postprocedural respiratory disorders, not elsewhere classified				X
J96	Respiratory failure, not elsewhere classified				X
J98	Other respiratory disorders				X
J99	Respiratory disorders in diseases classified elsewhere				X
I110	Hypertensive heart disease with heart failure			X	
I130	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease			X	
I132	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease			X	
I50	Heart failure			X	

Supplementary Data 2: Case Definitions

Condition	Definition	Reference
Acute Lower Respiratory Tract Disease (aLRTD)	<p>Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, non-pneumonic lower respiratory tract infection (LRTI), acute bronchitis, exacerbation of underlying respiratory disease including asthma and chronic obstructive pulmonary disease (COPD), and cardiac failure with respiratory symptoms.</p> <p>Pneumothorax, pulmonary embolism, progression or new diagnosis of primary or secondary lung malignancy were excluded from aLRTD.</p>	
Pneumonia	<p>Pneumonia was defined as infection affecting the airways (below the level of the larynx), with either:</p> <ol style="list-style-type: none"> (1) an acute illness with radiographic shadowing which was at least segmental or present in more than one lobe and was not known to be previously present or due to other causes (2) in the absence of radiological investigation, clinical confirmation of pneumonic disease in the opinion of the treating physician 	Lim WS, Baudouin SV, George RC, <i>et al</i> ; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. <i>Thorax</i> . 2009 Oct;64 Suppl 3:iii 1-55.
Non-Radiologically Proven Lower Respiratory Tract Infection (NP-LRTI)	An infection that affects the airways (below the level of the larynx) including the trachea and alveoli, with neither the presence of radiological change nor a clinical diagnosis of pneumonia from the treating physician, i.e. non-pneumonic infection in the lungs.	Anderson W, Winter J. Managing LRTI in adults in the community. <i>Practitioner</i> . 2009 Nov;253(1723):21-5, 2-3. PMID: 20043506.
Cardiac/Heart Failure (HF)	A clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion.	Bozkurt, Biykem et al. Universal Definition and Classification of Heart Failure. <i>Journal of Cardiac Failure</i> , Volume 27, Issue 4, 387 – 413.
Other aLRTD	aLRTD which was neither pneumonia, NP-LRTI nor HF was classified as 'Other aLRTD'. This therefore includes non-infective exacerbations of chronic respiratory disease such as asthma, COPD and bronchiectasis	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 21-24
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	24
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21-24
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10-11, 21-24
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 21-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The incidence of acute lower respiratory tract disease hospitalizations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology

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Title: The incidence of acute lower respiratory tract disease hospitalizations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology

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Running Title: Incidence of acute lower respiratory tract disease in adults

Keywords: Pneumonia, respiratory infection, lower respiratory tract infection, heart failure

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1
2
3 Department of Health and Social Care. The remainder of the study funding
4
5 was from Pfizer, Inc (WI255886-1).
6
7

8 **Competing Interests:** EB, JS, JC, SG, and BG are full time employees of Pfizer Vaccines and hold
9
10 stock or stock options. CH is Principal Investigator of the Avon CAP study
11
12 which is an investigator-led University of Bristol study funded by Pfizer and
13
14 has previously received support from the NIHR in an Academic Clinical
15
16 Fellowship. AF is a member of the Joint Committee on Vaccination and
17
18 Immunization (JCVI) and chair of the World Health Organization European
19
20 Technical Advisory Group of Experts on Immunization (ETAGE) committee. In
21
22 addition to receiving funding from Pfizer as Chief Investigator of this study,
23
24 he leads another project investigating transmission of respiratory bacteria in
25
26 families jointly funded by Pfizer and the Gates Foundation. The other
27
28 authors have no relevant conflicts of interest to declare.
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33 **Word count:** 2997/4000
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38 **Summary (38/40 words):** Using both retrospective and prospective methodologies, we found a high
39
40 annual incidence of acute lower respiratory disease (>1700 per 100000; 1.7%) in and around Bristol,
41
42 UK: pneumonia (~0.6%), lower respiratory tract infection without pneumonia (>0.7%), and heart
43
44 failure (>0.3%).
45
46
47

48 **Author Contributions:** CH, EB, MGG, JS, BDG and AF generated the research questions and analysis
49
50 plan CH, EB, MGG, JS, JC, SG and BDG undertook and contributed to the data
51
52 analysis. AF oversaw the research and data collection which was undertaken by
53
54 CH and MGG. All authors contributed to the preparation of the manuscript.
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1 **Abstract (278/300):**

2 **Objectives**

3 To determine the disease burden of acute lower respiratory tract disease (aLRTD) and its subsets
4 (pneumonia, lower respiratory tract infection [LRTI], heart failure) in hospitalized adults in Bristol, UK.

5 **Setting**

6 Single-centre, secondary care hospital, Bristol UK

7 **Design**

8 We estimated aLRTD hospitalizations incidence in adults (≥ 18 years) in Bristol, UK using two
9 approaches. First, retrospective ICD-10 code analysis (first five positions/hospitalization) identified
10 aLRTD events over a 12-month period (March2018–Feb2019). Secondly, during a 21-day prospective
11 review (19Aug–9Sept2019), aLRTD admissions were identified, categorized by diagnosis, and
12 subsequently annualized. Hospital catchment denominators were calculated using linked general
13 practice and hospitalization data, with each practice's denominator contribution calculated based on
14 practice population and percent of the practices' hospitalizations admitted to the study hospital.

15 **Participants**

16 Prospective review: 1322 adults screened; 410 identified with aLRTD. Retrospective review: 7727 adult
17 admissions.

18 **Primary and Secondary outcome measures**

19 The incidence of aLRTD and its subsets in the adult population of Southmead Hospital, Bristol UK.

20 **Results**

21 Based on ICD-10 code analysis, annual incidences per 100000 population were: aLRTD, 1901;
22 pneumonia, 591; LRTI, 739; heart failure, 402. aLRTD incidence was highest among those ≥ 65 -years:
23 65–74 (3684 per 100000 adults), 75–84 (6962 per 100000 adults), and ≥ 85 (11430 per 100000 adults).

24 During the prospective review, 410/1322 (31%) hospitalized adults had aLRTD signs/symptoms, and
25 annualized incidences closely replicated retrospective analysis results.

26 **Conclusions**

27 aLRTD disease burden was high, increasing sharply with age. aLRTD incidence is probably higher than
28 estimated previously due to criteria specifying respiratory-specific symptoms or radiological change,
29 usage of only the first diagnosis code, and mismatch between case count sources and population
30 denominators. This may have significant consequences for healthcare planning, including usage of
31 current and future vaccinations against respiratory infection.

34 ***Strengths and Limitations of This Study***

- 35 • We used two analytical methods at the same site over a comparable period, to calculate
36 incidence using both prospective and retrospective approaches.
- 37 • The case burden of aLRTD and its subgroups was pre-defined and included patients with
38 atypical presentations
- 39 • We calculated incidence using a denominator derived from GP records, providing increased
40 accuracy compared to population calculations based on census data.
- 41 • This was a single-center study, with a predominantly Caucasian cohort; therefore, the findings
42 might not be generalizable to other populations.
- 43 • The ICD-10 coding data analysis was limited to codes within the first five positions, and
44 therefore may have excluded some cases where other diagnoses were placed higher in the
45 diagnostic coding hierarchy.

47 Introduction

48 Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, non-pneumonic lower
49 respiratory tract infection (NP-LRTI), acute bronchitis, exacerbation of underlying respiratory diseases
50 (including asthma and chronic obstructive pulmonary disease [COPD]), and acute heart failure (HF)
51 events resulting in respiratory symptoms (e.g. breathlessness). Before the COVID-19 pandemic,
52 European healthcare costs for pneumonia alone in adults were estimated at €10 billion annually,
53 including €5.7 billion for inpatient care. [1] Pneumonia incidence in Europe varies by country and intra-
54 country region, age, socioeconomic status, and gender; [2-4] however, in all studies pneumonia
55 incidence in adults increases sharply with age. [3] Pneumonia affects an estimated 0.5% to 1% of UK
56 adults each year [5, 6]. Overall LRTI incidence is considerably higher with ~15% of UK adults aged ≥65
57 years experiencing an event each year.[7] Whilst HF is not typically clinically included as an acute
58 respiratory illness, HF with respiratory symptoms may be caused by respiratory viral infection, such as
59 respiratory syncytial virus (RSV), either acutely or 3-4 weeks after the primary infection [8, 9].

60
61 However, aLRTD incidence may be considerably higher than previously reported, given that published
62 literature has documented several reasons why previous estimates may have been erroneously low
63 [1]. Estimates of aLRTD based on pneumonia defined as radiologically demonstrated alveolar
64 infiltrates, may underestimate true disease burden as chest radiography (CXR) is an imperfect gold-
65 standard. [10, 11] Immunosuppressed, elderly or dehydrated patients are likely to be under-
66 represented if respiratory infection is defined by radiologically demonstrated changes. [10, 11]
67 Microbiological investigations for pneumonia are undertaken variably and identify a causative
68 pathogen in 50% of cases at most [12, 13]; hence, the disease is probably under-reported when
69 confirmed microbiological diagnosis is required. Furthermore, Respiratory Syncytial Virus (RSV)
70 infection has recently been recognized as an important respiratory pathogen later in life, [9] with
71 severe disease occurring in patient groups in whom the diagnosis is likely to be under-recognized (e.g.

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3 72 the elderly or those with underlying cardiac conditions). [8] Studies of clinical coding data are
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5 73 retrospective and subject to recognized limitations associated with this methodology [14, 15]. Older
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7 74 patients with pneumonia often have atypical presenting signs and symptoms, which may lead to
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9 75 missed or incorrect admission diagnoses. [16] Pneumonia may occur secondary to, or be an underlying
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11 76 cause of, the main presenting complaint, particularly in patients with cerebrovascular accidents (CVA),
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13 77 HF, COPD exacerbations or altered consciousness levels. [17] In these scenarios, pneumonia may not
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15 78 be the primary hospitalization diagnosis code and may not even be coded as an associated diagnosis.
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22 80 There are many studies examining the incidence of acute respiratory illness in children; however, data
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24 81 on respiratory illness in adults in the UK is lacking. Given the paucity of data supporting accurate aLRTD
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26 82 incidence rates and its disease subsets in adults, we undertook to assess aLRTD incidence by two
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28 83 approaches (retrospective and prospective) in Bristol, UK, seeking to determine the disease burden of
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30 84 hospitalized aLRTD and its subgroups more accurately.
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86 **Methods**

87 *Study Design*

88 This study was conducted at a large secondary care institution in UK (North Bristol NHS Trust) with
89 specialist Respiratory Services (interstitial lung disease, pleural disease). Two approaches were
90 undertaken to estimate aLRTD incidence: (1) “retrospective analysis” of aLRTD International
91 Classification of Diseases Tenth Revision (ICD-10) diagnostic codes for an entire year; and, (2) 21-day
92 observational “prospective review” of aLRTD hospital admissions.

93 *Ethics*

94 This study was approved by North Bristol NHS Trust Research Audit Ethics Committee (CA52218). Data
95 were anonymized before the authors accessed them for the purpose of this study.

96 *Patient and Public Involvement*

97 No patient involved.

98 *Retrospective Analysis*

99 For the retrospective analysis, all adult inpatient admissions (≥ 18 years) obtained from Hospital
100 Episode Statistic (HES) to the study hospital during March 2018–February 2019 with aLRTD ICD-10
101 diagnostic codes (Supplementary data 1) in any of the first 5 positions were identified and categorized
102 into aLRTD subgroups: pneumonia, NP-LRTI, other LRTD, and HF (Supplementary data 2). A mutually
103 exclusive hierarchy was used (pneumonia, NP-LRTI, then other LRTD) although HF diagnoses could co-
104 occur with other categories. “Other LRTD” included acute respiratory events that could not definitively
105 be placed in another category. Only the first 5 ICD-10 codes were available for analysis.

106 *Prospective Review*

107 Adult patients (≥ 18 years) resident within Bristol, North Somerset, and South Gloucestershire Clinical
108 Commissioning Group (CCG) referred to the Acute Medical Unit (AMU) at North Bristol NHS Trust

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3 109 during 19th August –9th September 2019 were included in an audit on acute respiratory illness. This
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5 110 time period was selected because it was felt to represent a period when there were an average
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7 111 number of adults hospitalised with aLRTD. A respiratory physician (CH) reviewed presenting features
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9 112 and investigation results for each admitted patient to determine whether aLRTD was present. Further
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11 113 medical record review was undertaken if patients had: new/worsening breathlessness, cough or
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13 114 sputum production; new or worsening peripheral oedema; pleurisy; clinical examination findings
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15 115 consistent with respiratory infection or HF; or fever attributable to suspected respiratory infection.
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17 116 Patients with non-respiratory diagnoses were excluded. There were no patient refusals for either
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19 117 approach.
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24 118 *Prospective Review Outcome measures*

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27 119 aLRTD was considered confirmed in individuals with: new/worsening respiratory symptoms, with or
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29 120 without fever; sepsis, delirium or raised inflammatory markers attributable to likely respiratory
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31 121 infection in admitting clinical team's opinion; radiological change in keeping with infection (e.g.
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33 122 consolidation); and/or final diagnosis of NP-LRTI, pneumonia or infective exacerbation of a chronic
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35 123 respiratory condition. A pneumonia diagnosis was assigned if radiological changes likely due to
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37 124 infection were described by the reporting radiologist. An NP-LRTI diagnosis was assigned if aLRTD signs
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39 125 and symptoms likely to be due to infection were present without demonstrated radiological change.
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41 126 A HF diagnosis was assigned in presence of: new/worsening breathlessness and bi-basal crepitations,
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43 127 cardiac wheeze or new/worsening bilateral pitting oedema; elevated pro-NT BNP (≥ 450 pg/mL);
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45 128 radiologist-reported radiographic changes consistent with cardiac failure; or a final consultant
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47 129 physician diagnosis of HF, cardiac failure or left-ventricular failure. When present, ≥ 1 diagnosis was
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49 130 selected.
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54 131 For both retrospective and prospective studies, pneumonia included both community and healthcare
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56 132 setting acquired cases; although, the prospective review only captured admitting diagnoses and
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58 133 pneumonias occurring later during hospitalization were not included.
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3 134 *Incidence calculations*
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6 135 Annual incidence per 100000 persons was calculated for both retrospective and prospective studies.
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8 136 Case counts from prospective review were annualized (i.e., case counts by diagnosis and overall were
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10 137 divided by the percentage of annual admissions for these diagnosis groups that occurred in this 21-
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13 138 day period in the retrospective analysis).
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16 139 *Incidence Denominators*
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19 140 To calculate appropriate population denominators for incidence calculations, aLRTD hospital
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21 141 admission event data were linked to aggregated GP practice patient registration data within the NHS
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23 142 Bristol, North Somerset, and South Gloucestershire CCG for 2017–2019. Only 4% of patients sought
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25 143 care at North Bristol NHS Trust hospital from outside these local CCGs, despite presence of specialist
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27 144 respiratory services. In the UK, GP registration is available free of charge for all, regardless of
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29 145 residential status. For GP practices within these same CCGs, the proportion of their aLRTD admissions
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31 146 occurring at North Bristol NHS Trust was multiplied by their patient registration count in 2019 by age
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33 147 group, to get each practice's contribution to the denominator (e.g. if 50% aLRTD admissions were at
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35 148 North Bristol among persons 50–64 years, the practice would contribute half of their patients 50–64
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37 149 years to the denominator). Further details of this methodology have been described previously. [18]
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44 151 *Statistical analysis*
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47 152 Patient characteristics were tabulated by aLRTD diagnosis. Categorical variables were presented as
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49 153 counts with percentages. Continuous data are presented with means and standard deviations (SD) if
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51 154 normally distributed and medians and interquartile range (IQR) if not normally distributed. Patient
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53 155 groups difference were evaluated using the Friedman test with Wilcoxon signed-rank test.
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157 **Results**

158 *Retrospective analysis*

159 Over a 12-month period, we identified 7727 hospital admissions for aLRTD: 3005 NP-LRTI admissions,
160 2402 pneumonia, 1633 HF and 1071 other LRTD (Table 1). aLRTD admissions were lowest in March
161 and April and highest December through February (Figure 1A), overall and for all aLRTD subgroups
162 ($P<0.05$) (Figure 1B-D). Overall, 28.1% (2244) cases were identified as being potentially hospital-
163 acquired infection based on co-occurring ICD-10 code 'Y95 Nosocomial Infection'.

165 *Prospective review*

166 Among 1322 eligible adult patients referred to AMU over the 21-day review period (Figure 2), 410
167 patients had signs or symptoms of aLRTD: 188 (46%) NP-LRTI; 152 (37%) pneumonia, and 77 (19%) HF.
168 Seven patients had both decompensated HF and a respiratory infection at hospital admission. On
169 admission, >10% of aLRTD patients did not have respiratory symptoms: 16 (11%) pneumonia, 25 (13%)
170 NP-LRTI, and 18 (14%) HF (Table 2).

171 Almost all adults admitted with aLRTD underwent routine biochemistry, hematology, and radiological
172 investigation (99.9%, $n=409$). In contrast, only 150 (37%) patients with aLRTD had microbiological
173 testing performed: blood cultures ($n=149$, 36%) and urine cultures ($n=143$, 35%). Pneumonia patients
174 more commonly underwent microbiological investigation than NP-LRTI patients ($P<0.05$) with highest
175 disparity in rates of sputum culture, urinary antigens, and respiratory viral PCR (Table 2). All cardiac
176 failure patients who underwent microbiological investigation had concomitant respiratory infection
177 (Table 2). Overall, a microbiological diagnosis was found in 11 (3%) cases, highlighting the low
178 frequency of definitive pathogen identification in aLRTD. Younger patients underwent microbiological
179 testing more frequently than the elderly for all aLRTD categories (Table 2).

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3 181 *Disease incidence*
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6 182 Retrospective analysis yielded an overall aLRTD incidence of 1901 per 100000. Disease incidence rose
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8 183 with increasing age (Table 3), both overall and for all disease subgroups; incidences per 100000 among
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10 184 adults aged ≥ 85 years were: 11430 (aLRTD), 6116 (NP-LRTI), 4215 (pneumonia) and 4005 (HF). Overall,
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12 185 28.1% aLRTD hospitalizations also included an ICD-10 discharge code for 'nosocomial infection',
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14 186 suggesting the aLRTD event or other infection was hospital-acquired. For pneumonia 25.3% had the
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16 187 nosocomial infection code. If all of these were related to the pneumonia diagnosis, an estimated
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18 188 residual 1794 events would have been community-acquired pneumonia (annual incidence
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20 189 441/100000 adults). Among older age categories, where the incidence of aLRTD was highest, NP-LRTI
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22 190 incidence was similar to pneumonia incidence, with an approximate 1:1 ratio of NP-LRTI to pneumonia
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24 191 cases. However, among adults under age 50 years, there were approximately twice as many NP-LRTI
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26 192 cases observed as pneumonia cases. Incidence calculations using annualized prospective review
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28 193 results were broadly comparable with retrospective analysis of ICD-10 data (Table 3).
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3 194 **Discussion:**
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5 195 This is the first UK study to assess aLRTD incidence comprehensively. We conducted an analysis of 12-
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7 196 months of hospital admissions by ICD-10 diagnosis code data and a 21-day prospective review at a
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9 197 large academic hospital in southwest England. With both approaches, we found a high annual
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11 198 incidence of aLRTD (>1700 per 100000; 1.7%), pneumonia (~0.6%), NP-LRTI without pneumonia
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13 (>0.7%), and HF (>0.4%). Incidences increased sharply in a non-linear manner as age increased above
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15 199 65 years for all aLRTD categories. These results suggest rates are probably significantly higher than
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17 200 previous disease estimates from the UK (Table 4) but comparable with many results globally, [19, 20]
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19 201 with important consequences for healthcare resources. For example, a recent review highlighted that
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21 202 pneumonia incidences ranged from 1000 to 2500 per 100000 (1–2.5%) among persons aged 65–74
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23 203 years in Spain, Germany, France, Japan and the US, which are comparable to the >1250 per 100000
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25 204 (1.3%) reported here. Some of the potential sources of underestimation for other UK incidence studies
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27 205 (Table 4) include: case source and denominator mismatch; use of first position in ICD-code analysis
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29 206 only; inclusion of enrolled subjects in consent-based prospective studies only; requiring specific
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31 207 symptoms and chest x-ray confirmation in order to be classified as pneumonia/aLRTD; and, lastly, the
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33 208 rising incidence of aLRTD.
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42 211 *Comparison with published literature*
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45 212 No studies have reported aLRTD incidence comprehensively in UK hospitalized patients within the last
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47 213 20 years. However, eight publications report incidence of ≥ 1 aLRTD subgroup. Seven publications
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49 214 reported community-acquired pneumonia (CAP) incidence (three from Nottingham, UK). For
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51 215 pneumonia, our incidence estimates were three to four-fold higher than other UK inpatient incidence
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53 216 estimates (Table 4) but comparable to estimates from other countries. [19, 20] Only two UK studies
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55 217 from approximately 20 years ago reported NP-LRTI incidence (one with both CAP and NP-LRTIs; Table
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57 218 4), and only one provided an inpatient estimate. [21] NP-LRTI incidence was approximately 2-fold
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3 219 lower than that calculated here, taking into account inclusion of CAP and other NP-LRTI in their
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5 220 estimates. [21, 22] The one UK study reporting HF incidence had methodological differences (i.e.,
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7 221 inclusion of outpatients and limiting to initial HF diagnosis) and estimates could not be compared. [23]
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9 222 Close examination of the existing literature methods yielded multiple sources for potential
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11 223 underestimation.
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15 224 First, for incidence studies that were not countrywide, identifying an appropriate denominator is
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17 225 challenging. Like many other inpatient settings worldwide, UK hospitals' catchment areas for acute
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19 226 treatment are principally driven by geography, but the proportion of any area's residents expected to
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21 227 use the hospital becomes less clear as distance from the hospital increases because catchment areas
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23 228 and populations of different hospitals may overlap. Defining hospital catchment populations based
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25 229 solely on census data cannot account for this variability. Including all geographic areas using the
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27 230 hospital to any extent results in population denominator overestimation and underestimated
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29 231 incidence. Here, we addressed this by calculating population denominators based on hospital
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31 232 utilization behavior from referring General Practices.
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35 233 Second, other studies used fewer codes in their ICD code analysis: all limited their analyses to events
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37 234 where the diagnostic code was in the first position (Table 4; case definition column), potentially
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39 235 excluding admissions in which pneumonia/NP-LRTI complicated other underlying respiratory diseases,
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41 236 including COPD and asthma. Limiting to first position has been shown to reduce sensitivity for
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43 237 pneumonia events by about 30% (66%–72% sensitive). [22, 24] Conversely, the recent British Thoracic
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45 238 Society (BTS) audit on CAP found ~27% of pneumonia events identified by ICD code (J12-18) had no
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47 239 new CXR infiltrates. [6] Even accounting for this potential over coding practice, our estimates remain
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49 240 well above other published UK estimates.
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54 241 Third, for other prospective studies, exclusion of events where patients did not consent to
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56 242 participation or were not identified by study surveillance processes (often conducted predominately
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58 243 during business hours) can introduce underestimation. Further, other prospective pneumonia studies
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3 244 specifically required documentation of specific symptoms, radiological findings, and treatments, [25]
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5 245 potentially excluding those without these features documented in medical records. In our prospective
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7 246 review, approximately 11% did not display typical signs and symptoms of pneumonia and could have
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9 247 been excluded by that requirement. Requiring CXR confirmation has been shown to reduce incidence
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11 248 estimates for pneumonia, [20] although all pneumonia events in our prospective review were
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13 249 radiologically confirmed.
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17 250 Fourth, trends over time may also contribute to our estimates being higher than previous reports. Our
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19 251 study's estimates are recent, and rising incidence of pneumonia has been documented in all studies
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21 252 that have reported such trends. [25-27]
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24 253 Finally, this study included, in part, hospital-acquired pneumonias (HAP), which were excluded from
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26 254 estimates calculated in some other studies (Table 4). The retrospective analysis may have included
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28 255 more nosocomial infection than the prospective review, as the latter was focused on evaluation of
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30 256 patients at admission for aLRTD and would not have reliably captured events that developed during
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32 257 hospitalization. 25.3% pneumonia events included a nosocomial infection code, but this code could
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34 258 relate to any nosocomial infection during that hospitalization. If all these cases were assumed to be
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36 259 hospital-acquired pneumonia, our estimates community-acquired pneumonia incidence would still be
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38 260 well above prior UK estimates: 441/100000 (≥ 18 years).
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43 261 While not impacting all-cause aLRTD incidence estimates discussed above, during the prospective
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45 262 review, we found low rates of microbial investigation which prevented us from generating pathogen-
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47 263 specific incidence estimates. Only 52% of patients with radiologically-confirmed pneumonia
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49 264 underwent microbiological testing during hospitalization, with even lower rates in other aLRTD
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51 265 subgroups (41% NP-LRTI and 14% HF). Microbiological testing occurred less frequently as age
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53 266 increased, particularly in NP-LRTI patients. It is possible that, because aLRTD hospitalizations are
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55 267 substantially more common among older persons, less etiologic investigation is performed.
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57 268 Furthermore, clinicians may elect to treat elderly patients with a more pragmatic and less invasive
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3 269 approach. Management guidelines do not require specific pathogen identification to inform treatment
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5 270 choice. Presence only of atypical features on presentation (in this series, 13% NP-LRTI and 11%
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7 271 pneumonia cases) may also reduce the likelihood of timely microbiological testing. Low rates of
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9 272 microbiological testing, and consequently of confirmed microbiological diagnosis, may represent a
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11 273 source of underestimation of pathogen-specific disease incidence in patient groups (i.e., testing bias),
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13 274 particularly in elderly patient groups.
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20 276 *Strengths and Limitations of This Study*

23 277 This study has many strengths. First, this study used two analytical methods at the same site over a
24
25 278 comparable period, to calculate incidence using both prospective and retrospective approaches.
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27 279 Second, the case burden of aLRTD and its subgroups was pre-defined and included patients with
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29 280 atypical presentations but with clinical and/or radiological diagnoses, who may otherwise have been
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31 281 excluded from analysis. Additionally, we calculated incidence using a denominator derived from GP
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33 282 records, providing increased accuracy compared to population calculations based on census data.
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37 283 However, the study also had some limitations. This was a single-center study, with a predominantly
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39 284 Caucasian cohort; therefore, the findings might not be generalizable to other populations both within
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41 285 the UK and in other countries. Different healthcare systems may affect patient treatment preference,
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43 286 and as the NHS provides care which is free at the point of access, the hospitalization rates seen in this
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45 287 study may be different in fee or insurance based healthcare system. Similarly, physician treatment
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47 288 preferences may affect hospitalization rates, and we have not explored these in this analysis. The ICD-
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49 289 10 coding data analysis was limited to codes within the first five positions, and therefore may have
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51 290 excluded some cases where other diagnoses were placed higher in the diagnostic coding hierarchy.
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53 291 Furthermore, we could not determine how many cases of the 28.1% ICD-10 cases also coded with
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55 292 nosocomial infection had hospital-acquired respiratory infection rather than other nosocomial
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57 293 infections.
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3 294 Although the denominator used to calculate incidence was derived from GP records, this was still an
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5 295 estimate as there is no precisely defined denominator hospital catchment. We were unable to exclude
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7 296 patients from outside the local CCGs in the retrospective analysis, due to the way ICD-10 data was
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10 297 obtained. However, these patients were excluded from the prospective review and the incidence
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12 298 calculated was comparable, suggesting any effect that patients attending North Bristol NHS Trust from
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14 299 outside the local CCGs have on incidence estimates is minimal. This may be because any effect of
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16 300 travelling or health-seeking behavior is bi-directional: whilst some patients admitted to Southmead
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18 301 hospital were from outside the local area, it is also true that patients with aLRTD within the relevant
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20 302 CCGs would have been admitted to other hospitals. We also acknowledge the 21-day prospective
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22 303 review period was relatively short, not repeated and may not be fully representative of clinical practice
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24 304 and cases throughout the year. This study was conducted before the emergence of COVID-19, and we
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26 305 think these data will be useful in one of two ways in the context of COVID-19: (1) either COVID-19 will
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28 306 become endemic, and the data will reflect the first year before a new normal, or (2) COVID-19 will
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30 307 abate and it will provide an anchor for understanding incidence during a respiratory viral pandemic'
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38 309 In conclusion, we found similarly high estimates of LRTD incidence using two different approaches,
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40 310 and these estimates were higher than those obtained previously in the UK. Determining if there is a
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42 311 real increase in incidence, or if this estimate is larger due to more accurate methodology including a
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44 312 more accurate denominator will require ongoing comprehensive surveillance. Nonetheless,
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46 313 combining all types of LRTD highlights the high burden for this important and potentially life-
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48 314 threatening disease group. Incidence assessments require close assessments of potential areas of
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50 315 under ascertainment, including unidentified or unenrolled cases in prospective studies, reduced
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52 316 positions or number of ICD-10 codes included for retrospective studies, and population denominator
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54 317 mismatch for all study types. Our prospective review findings highlight the need to consider atypical
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56 318 clinical presentations for pneumonia and the lack of routine microbiological investigation in many
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3 319 aLRTD patients required for pathogen-specific aLRTD incidence calculation. Future research should
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5 320 include a fully prospective assessment of aLRTD incidence with comprehensive diagnostic testing
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7 321 across multiple respiratory seasons, to ensure accurate capture of all aLRTD events, particularly in the
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9 322 elderly. Such research should be undertaken given the high and rising aLRTD burden to enable
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11 323 appropriate healthcare planning and identification of interventions which may reduce disease burden.
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For peer review only

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10
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12
13 330 Harvey Walsh Limited.
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18 332 **Data Sharing**
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20 333 No additional data available
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Table 1: Demographic Characteristics of Patients admitted with aLRTD for 1 Year ICD-10 code Retrospective Analysis and 21-day Prospective Review**Period -- 2018–2019**

Characteristic	Pneumonia		NP-LRTI		Heart Failure		Other LRTD	All LRTD	
	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Retrospective Review Only	Prospective review	Retrospective analysis
N	152	2402	188	3005	77	1633	1071	410	7727
Gender, females	61 (40)	1078 (45)	99 (53)	1482 (49)	39 (51)	731 (45)	489 (46)	194 (47)	3780 (49)
Age									
Median (IQR), y	80 (67-86)	81 (66-88)	70 (46-87)	69 (45-87)	87 (72-90)	87 (70-90)	74 (53-82)	80 (64-88)	81 (65-90)
18-24	4 (3)	72 (3)	9 (5)	151 (5)	0 (0)	0 (0)	26 (2)	13 (3)	249 (3)
25-34	2 (2)	48 (2)	12 (6)	183 (6)	0 (0)	3 (0)	33 (3)	14 (3)	267 (3)
35-44	6 (4)	97 (4)	14 (7)	209 (7)	2 (3)	10 (1)	59 (6)	22 (5)	375 (5)
45-54	8 (5)	118 (5)	11 (6)	183 (6)	0 (0)	22 (1)	112 (10)	19 (5)	435 (6)
55-64	18 (12)	293 (12)	19 (10)	305 (10)	8 (10)	158 (10)	210 (20)	45 (11)	966 (13)
65-74	34 (22)	501 (21)	32 (17)	549 (18)	10 (15)	199 (12)	223 (21)	75 (18)	1472 (19)
75-84	44 (28)	667 (28)	40 (21)	621 (21)	20 (30)	498 (31)	205 (19)	100 (24)	1991 (26)
≥85	38 (26)	606 (25)	51 (27)	704 (23)	37 (55)	742 (45)	203 (19)	123 (30)	2255 (29)

Table 2. Clinical Characteristics and Investigations of Patients admitted with aLRTD over 21-day Prospective Review Period in August-September 2020

Characteristic	Pneumonia n=152 (%)	NP-LRTI n=188 (%)	Heart Failure n=77 (%)	All LRTD n=410 (%)
GP	56 (37)	72 (39)	30 (39)	158 (39)
A&E department	93 (61)	100 (54)	45 (58)	238 (58)
Transfer from another unit	2 (1)	13 (7)	0 (0)	15 (4)
Other	1 (1)	1 (1)	2 (3)	4 (1)
Referral Source				
Typical features†	136 (89)	163 (87)	63 (82)	355 (87)
Atypical features	16 (11)	25 (13)	14 (18)	55 (13)
- collapse/falls	11 (7)	12 (6)	0 (0)	23 (6)
- confusion	0 (0)	7 (4)	4 (5)	10 (2)
- drowsiness	1 (1)	1 (1)	2 (3)	4 (1)
- off legs/generally unwell	5 (3)	5 (3)	8 (10)	18 (4)
LRTD Signs and symptoms on referral to AMU				
Biochemistry	152 (100)	185 (99)	77 (100)	419 (100)
Haematology	152 (100)	185 (99)	77 (100)	419 (100)
Radiology	152 (100)	185 (99)	77 (100)	419 (100)
Investigations Performed				
<i>Testing by Age Group</i>				
All patients	79/152 (52)*	77/188 (41)	11/77 (14)	167 (41)
18-24	3/4 (75)	6/9 (66)	0/0 (0)	9/13 (69)
25-34	0/0 (0)	6/12 (50)	0/0 (0)	6/12 (50)
35-44	5/6 (83)	10/14 (71)	2/2 (100)	17/22 (77)
45-54	6/8 (75)	6/11 (55)	0/0 (0)	13/19 (68)
55-64	11/18 (61)	12/19 (63)	5/8 (63)	31/45 (69)
65-74	15/34 (44)	12/32 (38)	1/10 (10)	28/75 (37)
75-84	21/43 (49)	10/40 (25)	2/20 (10)	33/100 (33)
≥85	18/39 (46)	15/51 (19)	1/37 (3)	34/124 (27)
Test performed				
Blood culture	79 (52)	70 (37)	5 (6)	150 (37)
Urine culture	66 (43)	77 (41)	11 (14)	150 (37)
Sputum culture	27 (18)*	7 (4)	2 (3)	35 (9)
BinaxNOW® Pn UAT ‡	29 (19)*	6 (3)	0 (0)	35 (9)
Respiratory virus PCR	16 (11)*	11 (6)	1 (1)	28 (7)
Pleural fluid culture	3 (2)	0 (0)	1 (1)	4 (1)

A&E, Accident and Emergency department; GP, general practitioner; LRTD, lower respiratory tract disease; NP-LRTI, non-pneumonic lower respiratory tract infection; IQR, interquartile range; Pn UAT, pneumococcal urinary antigen test; PCR, polymerase chain reaction.

* $P < 0.05$.

† Typical symptoms included cough, breathlessness, increased or discolored sputum production, wheeze, pleurisy, peripheral oedema, haemoptysis, reduced exercise tolerance and/or fever.

‡ BinaxNOW Pn UAT was only performed in accordance with NICE/BTS guidelines.

Table 3: Incidence of aLRTD resulting in hospital admission based on prospective and retrospective approaches by age group and condition, North Bristol National Health Service Trust— United Kingdom 2018–2019.

	Age Groups					
	All Adults	18-49 y	50-64 y	65-74 y	75-84 y	≥85 y
Population in 2018	406481	226920	91534	45705	29487	12835
Retrospective Analysis of a Year's ICD-10 codes						
Annual cases – N (row %)						
All aLRTD	7,727	1,130 (14)	1,103 (14)	1,684 (22)	2,053 (27)	1,757 (23)
Pneumonia	2,402	264 (11)	288 (12)	589 (25)	720 (30)	541 (22)
NP-LRTI	3,005	576 (19)	410 (14)	572 (19)	662 (22)	785 (26)
Other LRTD	1,071	246 (23)	268 (25)	226 (21)	200 (19)	131 (12)
Heart Failure	1,633	48 (3)	189 (12)	397 (24)	485 (30)	514 (31)
LRTI/Pneumonia Ratio	1.3	2.2	1.4	1.0	0.9	1.5
Incidence (per 100,000)						
All aLRTD	1,901	497	1,205	3,684	6,962	13,689
Pneumonia	591	116	315	1,289	2,442	4,215
NP-LRTI	739	254	448	1,252	2,245	6,116
Other LRTD	263	108	293	494	678	1,021
Heart Failure	402	21	206	869	1,645	4,005
21-day Prospective Review (annualized)						
Annualized cases – N (row %)						
All aLRTD	7,885	1,038	962	1,692	2,231	1,962
Pneumonia	2,621	224	397	776	690	534
NP-LRTI	3,857	796	531	653	1,061	816
Heart Failure	2,000	51	205	308	641	795
LRTI/Pneumonia Ratio	1.5	3.6	1.3	0.8	1.5	1.5
Incidence (per 100,000)						
All aLRTD	1,940	458	1,050	3,703	7,565	15,283
Pneumonia	645	99	433	1,698	2,339	4,164
NP-LRTI	944	351	580	1,429	3,599	6,360
Heart Failure	492	23	224	673	2,174	6,193

LRTI = lower respiratory tract infection; LRTD = lower respiratory tract disease.

Pneumonia category includes community and healthcare acquired. For retrospective ICD-10 based cohort, the following mutually exclusive hierarchy was used to define pneumonia, LRTI, and other LRTD; heart failure event could overlap with other categories.

"Other LRTD" contains LRTD events that could not definitively be placed in one of the other respiratory disease categories.

Table 4: Literature review of aLRTD incidence in hospitalized adults, United Kingdom

Study	Study Years	Location (Facility)	Event Setting	Age	Case Definition ^b	Key inclusion	Denominator Source	Overall Incidence	Age Breakdown (years)	Incidence per 100,000 by age ^d	Comments
Community-acquired Pneumonia											
Current Study	2018 – 2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms with radiological change in keeping with infection (prospective review portion) AND Retrospective ICD-10 code analysis (1 st 5 positions): J12-J18, J85, and J86	Hospital-acquired pneumonia (HAP) included	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	648	18 –49	116	Retrospective analysis includes 1 st 5 positions
									50 –64	315	
								591	65 –74	1,289	
									75 –84	2,442	
								≥85	4,215		
Elston 2012, Epidemiol Infect	2002 – 2009	Hull and East Yorkshire Hospitals ^c	Inpatients only	≥16 y	ICD-10 codes (1 st position only): J18.0, J18.9, J13X, J18.1, and J15X	HAP included	Mid-year population estimates for Hull (city) and EroY (Surrounding County) from Office for National Statistics	143 (2002) – 207 (2009)	15 –64	48.8 – 84.1	Fewer ICD-10 codes included than other analyses; Y95 Nosocomial infection included.
								≥65	543 – 781		
Millet 2013, J Clin Epidemiol	1997 – 2011	UK	Both inpatients and outpatients	≥65 y	Read and ICD 10 codes; no specified codes provided. For ICD-10, used first diagnosis code for first episode of hospitalization only.	HAP Excluded	Mid-year UK population estimates from Office for National Statistics	799	65 –69	281	Incidence estimates converted to per 100,000 person-years
									70 –74	431	
									75 –79	694	
									80 –84 y	1,205	
									85 –89	2,184	
								≥90	4,194		
Pick 2020, Thorax ^a	2013 – 2014	Nottingham (2 large university hospitals)	Inpatients only	≥16 y	Inclusion criteria: one or more symptom suggestive of LRTI (defined as cough, increasing dyspnea, sputum production and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP Exclusion criteria: hospitalization within 10 days of index admission, a diagnosis of tuberculosis or post-obstructive pneumonia.	HAP Excluded	Mid-year estimates for the Greater Nottingham area from the Office for National Statistics, including local population data stratified by age group	96.3	16 –49	27.3	Only consented/enrolled subjects included in estimates Required CXR - confirmation but not all LRTI patients had CXR Census-derived denominator that may not have fully matched catchment area.
									50 –64	80.2	
								65 –74	181.3		
								75 –84	400.6		
								≥85	707.5		
	2017 – 2018							158.4	16 –49	29.9	
									50 –64	146.9	

								120.4	65–74 75–84 ≥85	310.4 559.5 1522.6	Required specific symptoms and evidence of treatment and some CAP events may not have had this information documented
	2013–2018							--	--	--	
Thorrington 2019, BMC Med	2004–2005 2014–2015	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J18 (pneumonia of unspecified causative organism)	HAP Included	Mid-year population estimates for England for 2004 to 2015 from Office for National Statistics	NA	≥65	829	Incidence is per 100,000 person-years. Fewer ICD-10 codes included than other analyses
									≥65	1787	
Trotter 2008, EID	1997–1998	England	Inpatients only	≥65 y	ICD 10 codes (1 st position only): J12–J18	HAP Included	Mid-year population estimates for England for 1997 to 2004 from the Office for National Statistics	NA	65–74 75–84 ≥85	263 684 1599	Incidence estimates converted to 100,000 population
	2004–2005								65–74 75–84	355 877	
									≥85	2218	
Lower Respiratory Tract Infection						Pneumonia					
Current Study	2018–2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change AND Retrospective ICD-10 code analysis: J09, J10, J11; J20, J21, J22, J40, J41, J42, J44, J45, and J46	Excludes all Pneumonia	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	802	18–49 50–64 65–74	254 448 1,252	
								739	75–84 ≥85	2,442 6,116	
Loving 2001, Clinical Micro. & Infection	1994–1996	Bristol (Southmead Hospital)	Inpatients only	≥16 y	LRTI episodes from four groups by ICD 9/10 codes: (1) CAP; (2) chest infection or acute exacerbation in presence of asthma; (3) chest infection or acute exacerbation in presence of COPD; or (4) bronchitis with no radiological evidence of pneumonia or pre-existing respiratory disease, such as COPD or asthma. No specified codes provided.	Includes Community-acquired Pneumonia HAP Excluded	No information on denominator provided	623	16–39 40–49 50–59 60–69 70–79 >79	151 175 294 1,086 2,135 3,141	Incidence converted to per 100,000 population Study involved single hospital and no mention of source of denominator mentioned.
Millet	1997–	UK	Both	≥65 y	Read and ICD 10 codes; no specified	Includes	Mid-year UK population	12,293	65–69	9,221	Incidence

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2013, J Clin Epidemiol	2011	inpatients and outpatients	codes provided. For ICD-10, used first diagnosis code for inpatient episode only.	Community-acquired Pneumonia	estimates from Office for National Statistics. (Patients were not considered at risk for community-acquired LRTI during an LRTI illness-episode, during a HES hospitalization, or for 14 days after any HES hospitalization or CPRD hospital code. This person-time was excluded from denominator.)	70–74 75–79 80–84 85–89 ≥90	10,740 12,607 15,137 18,791 26,287	converted to per 100,000 person years
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Heart Failure											All or First Episode		
Current Study	2018-2019	Bristol (Southmead Hospital)	Inpatients only	≥18 y	Clinical signs/symptoms of heart failure or elevated pro-NT BNP or radiological change	All	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for percent of admissions that came to Southmead.	328	18–49 50–64 65–74 75–84 ≥85	21 206 869 1,645 4,005			
					AND Retrospective ICD-10 code analysis: I110; I130; I132; I50			402					
Uijl 2019, Eur J Heart Fail	2000 – 2010	UK	Both inpatients and outpatients	≥55 y	4 sources of HER were linked: CPRD primary care records, HES secondary care hospital charges, Myocardial Ischaemia National Audit Project (MINAP) disease registry, and ONS national death registry. HES ICD-10 codes: Heart failure: I110, I130, I132, I260, I50 and I21. Individuals were excluded if they presented a history of HF before their index date in CPRD, HES or MINAP.	First episode at 55 years or older counted	Not Reported	Not Reported	55–64, M 55–64, F 65–74, M 65–74, F >75, M >75, F	360 190 1,360 920 3,440 2,800	Incidence converted to per 100,000 person years Included first episode of HF (inpatient or outpatient) at age 55 and up, so repeat episodes not included.		

^a Only the most recent incidence estimates from the Nottingham CAP study were included.

^b Add text names for all listed ICD codes in this footnote or appendix.

^c Included hospitals were Hull Royal Infirmary, Castle Hill Hospital, Princess Royal Hospital, Scarborough District General Hospital, Bridlington & District Hospital, York Teaching Hospital, Scunthorpe General Hospital, Goole & District Hospital.

^d For the current study, only age-group estimates from the retrospective analysis were included in this table, but these were closely comparable to the annualized incidence estimates based on the prospective review. See Table 3 for full results.

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3 **Figure Legends:**
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5 **Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North**
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8 **Bristol National Health Service Trust— United Kingdom 2018–2019.**

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10 Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower
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12 Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Non-pneumonic
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14 Lower Respiratory Tract Infection (NP-LRTI) (white bars), (D) Other LRTD (cross-hash bars), and (E)
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16 Heart Failure (grey bars).
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21 **Figure 2: Flow diagram of the Prospective Review**
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For peer review only

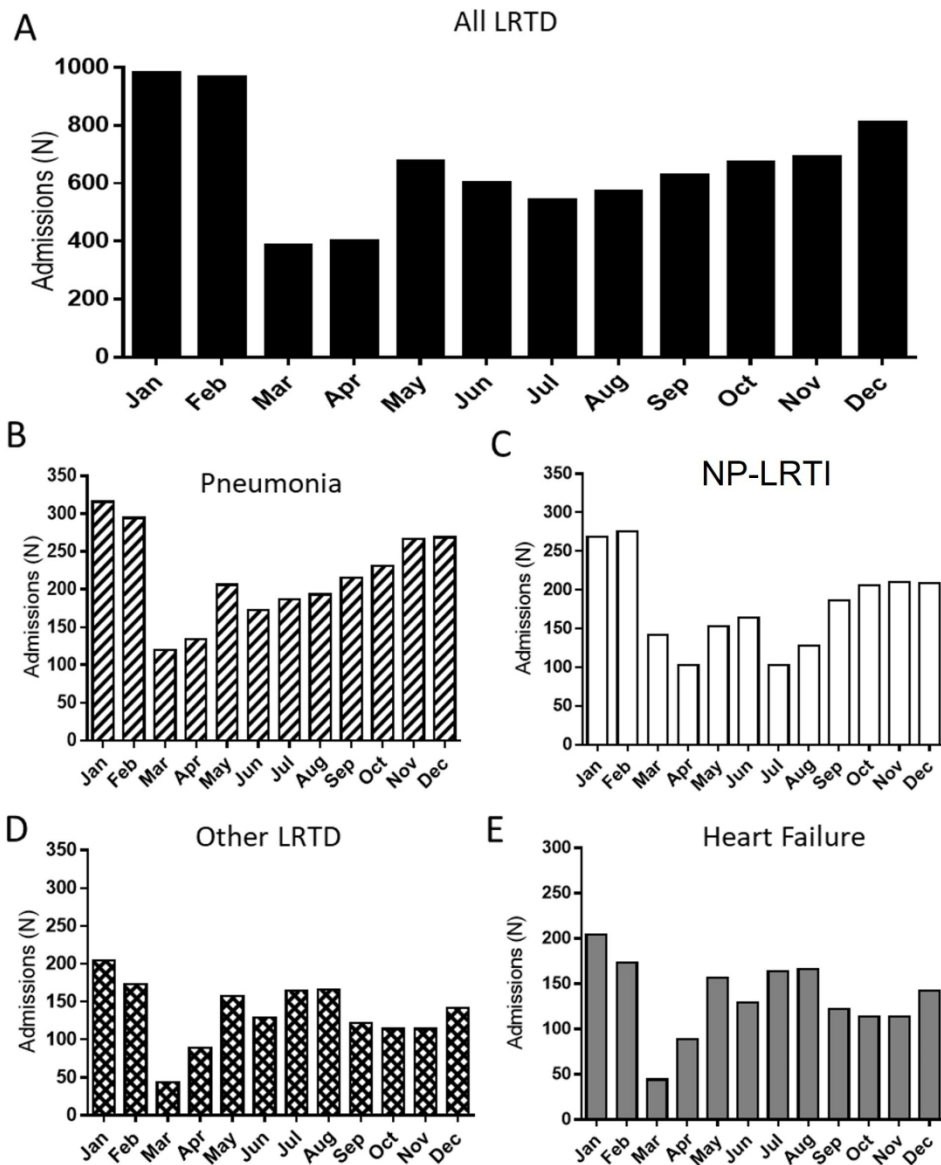


Figure 1: aLRTD admissions identified by Retrospective ICD-10 diagnostic code analysis at North Bristol National Health Service Trust— United Kingdom 2018–2019. Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute Lower Respiratory Tract Disease (aLRTD) (black bars), (B) Pneumonia (slashed bars), (C) Non-pneumonic Lower Respiratory Tract Infection (NP-LRTI) (white bars), (D) Other LRTD (cross-hash bars), and (E) Heart Failure (grey bars).

169x207mm (300 x 300 DPI)

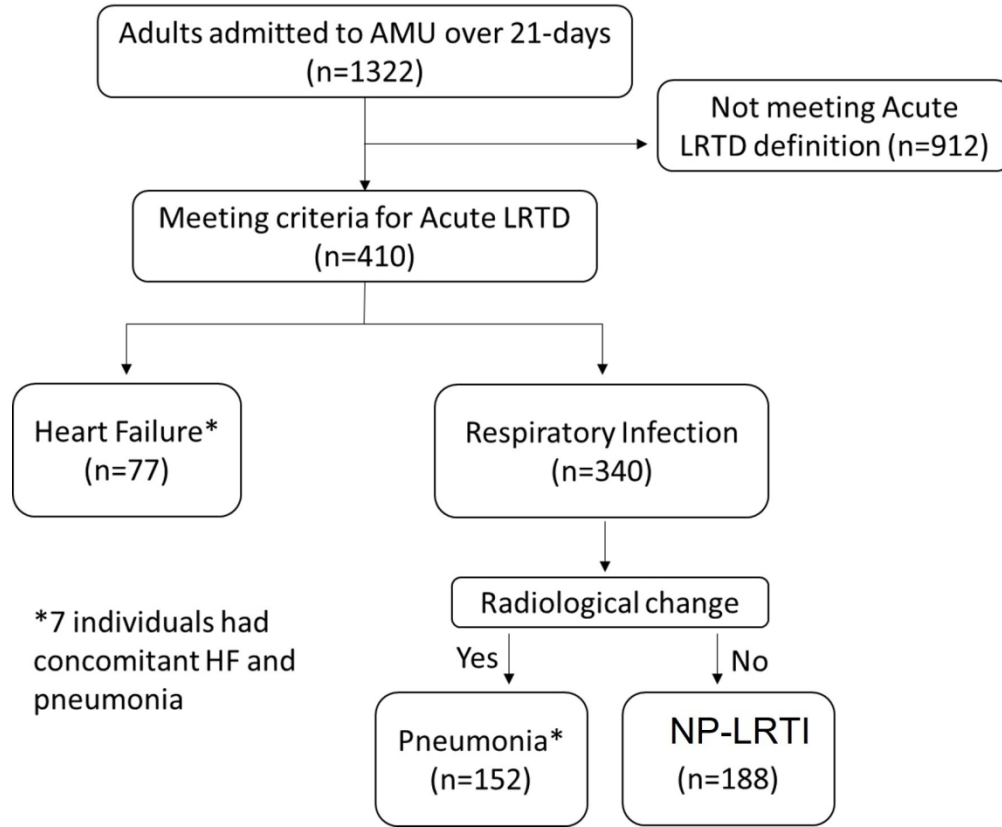


Figure 2: Flow diagram of the Prospective Review

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Supplementary Data 1: ICD-10 codes used for patient identification for Retrospective Analysis

ICD-10 code	Definition	Pneumonia	NP-LRTI	HF	Other aLRTD
J09	Influenza due to identified zoonotic or pandemic influenza virus		X		
J10	Influenza due to identified seasonal influenza virus		X		
J11	Influenza, virus not identified		X		
J12	Viral pneumonia, not elsewhere classified	X			
J13	Pneumonia due to <i>Streptococcus pneumoniae</i>	X			
J14	Pneumonia due to <i>Haemophilus influenzae</i>	X			
J15	Bacterial pneumonia, not elsewhere classified	X			
J16	Pneumonia due to other infectious organisms, not elsewhere classified	X			
J17	Pneumonia in diseases classified elsewhere	X			
J18	Pneumonia, organism unspecified	X			
J20	Acute bronchitis		X		
J21	Acute bronchiolitis		X		
J22	Unspecified acute lower respiratory infection		X		
J40	Bronchitis, not specified as acute or chronic		X		
J41	Simple and mucopurulent chronic bronchitis		X		
J42	Unspecified chronic bronchitis		X		
J43	Emphysema				X
J44	Other chronic obstructive pulmonary disease (including J44.0 chronic		J44.0 only		X (J44.0)

	obstructive pulmonary disease with acute lower respiratory infection)				
J45	Asthma				X
J46	Status asthmaticus				X
J47	Bronchiectasis				X
J85	Abscess of lung and mediastinum		X		
J86	Pyothorax		X		
J90	Pleural effusion, not elsewhere classified				X
J91	Pleural effusion in conditions classified elsewhere				X
J95	Postprocedural respiratory disorders, not elsewhere classified				X
J96	Respiratory failure, not elsewhere classified				X
J98	Other respiratory disorders				X
J99	Respiratory disorders in diseases classified elsewhere				X
I110	Hypertensive heart disease with heart failure			X	
I130	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease			X	
I132	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease			X	
I50	Heart failure			X	

Supplementary Data 2: Case Definitions

Condition	Definition	Reference
Acute Lower Respiratory Tract Disease (aLRTD)	<p>Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, non-pneumonic lower respiratory tract infection (LRTI), acute bronchitis, exacerbation of underlying respiratory disease including asthma and chronic obstructive pulmonary disease (COPD), and cardiac failure with respiratory symptoms.</p> <p>Pneumothorax, pulmonary embolism, progression or new diagnosis of primary or secondary lung malignancy were excluded from aLRTD.</p>	
Pneumonia	<p>Pneumonia was defined as infection affecting the airways (below the level of the larynx), with either:</p> <ol style="list-style-type: none"> (1) an acute illness with radiographic shadowing which was at least segmental or present in more than one lobe and was not known to be previously present or due to other causes (2) in the absence of radiological investigation, clinical confirmation of pneumonic disease in the opinion of the treating physician 	Lim WS, Baudouin SV, George RC, <i>et al</i> ; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. <i>Thorax</i> . 2009 Oct;64 Suppl 3:iii 1-55.
Non-Radiologically Proven Lower Respiratory Tract Infection (NP-LRTI)	An infection that affects the airways (below the level of the larynx) including the trachea and alveoli, with neither the presence of radiological change nor a clinical diagnosis of pneumonia from the treating physician, i.e. non-pneumonic infection in the lungs.	Anderson W, Winter J. Managing LRTI in adults in the community. <i>Practitioner</i> . 2009 Nov;253(1723):21-5, 2-3. PMID: 20043506.
Cardiac/Heart Failure (HF)	A clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion.	Bozkurt, Biykem <i>et al</i> . Universal Definition and Classification of Heart Failure. <i>Journal of Cardiac Failure</i> , Volume 27, Issue 4, 387 – 413.
Other aLRTD	aLRTD which was neither pneumonia, NP-LRTI nor HF was classified as 'Other aLRTD'. This therefore includes non-infective exacerbations of chronic respiratory disease such as asthma, COPD and bronchiectasis	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 21-24
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	24
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21-24
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10-11, 21-24
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 21-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.