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Estimating the contribution of respiratory pathogens to acute exacerbations of COPD using routine data

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SUMMARY

Objectives: To characterise microbiology testing and results associated with emergency admissions for acute exacerbation of COPD (AECOPD), and determine the accuracy of ICD-10 codes in retrospectively identifying laboratory-confirmed respiratory pathogens in this setting.

Methods: Using person-level data from the Secure Anonymised Information Linkage Databank in Wales, we extracted emergency admissions for COPD from 1/12/2016 to 30/11/2018 and undertook linkage of admissions data to microbiology data to identify laboratory-confirmed infection. We further used these data to assess the accuracy of pathogen-specific ICD-10 codes.

Results: We analysed data from 15,950 people who had 25,715 emergency admissions for COPD over the two-year period. 99.5% of admissions could be linked to a laboratory test within 7 days of admission date. Sputum was collected in 5,013 (19.5%) of admissions, and respiratory virus testing in 1,219 (4.7%). Where respiratory virus testing was undertaken, 46.7% returned any positive result. Influenza was the virus most frequently detected, in 21.5% of admissions where testing was conducted. ICD-10 codes exhibited low sensitivity in detecting laboratory-confirmed respiratory pathogens.

Conclusions: In people admitted to hospital with AECOPD, increased testing for respiratory viruses could enable more effective antibiotic stewardship and isolation of cases. Linkage with microbiology data achieves more accurate and reliable case definitions.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by reduced lung function, resulting in progressive dyspnoea and acute exacerbations which necessitate hospital admission if severe. The majority of acute exacerbations of COPD (AECOPDs) are considered to have an infective aetiology,[1] and antibiotic use for this indication is frequent, even though a significant proportion are likely to have a viral trigger.

To develop, implement and evaluate interventions to reduce the burden of respiratory tract infections, pathogen-specific data establishing the frequency and consequences of infection in different populations is imperative. Thus far, the focus of many studies examining the burden of specific respiratory pathogens has been on children.[2–4] Impact on other risk groups, such as those with COPD, requires further study, especially since acute exacerbations of COPD are one of the commonest reasons for emergency hospital admission in the UK,[5] resulting in substantial morbidity, mortality and healthcare cost each year.

International Statistical Classification of Diseases and Related Health Problems (ICD) codes relating to respiratory pathogens are readily available in databases of routinely collected electronic health data and have therefore often been used for research purposes.[6–11] However, the accuracy of diagnostic coding is likely to vary depending on local practices, and not all pathogens map to a specific ICD code.

Large-scale linkage of microbiology data to other routinely collected health data, where possible, is likely to be the more accurate data source in establishing the burden of particular pathogens. Researchers who have had access to microbiology data report that they would have grossly underestimated respiratory pathogen-related hospital admissions had they relied on diagnosis codes alone.[12–15] However, such linkage is currently not possible in many regions, rendering person-level analyses using microbiology data

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unattainable. Further, even in regions where such linkage is possible, the likelihood of successful linkage may vary depending on age, duration of hospitalisation, ethnic group and rurality.[16]

In this national study, we utilise linkable, routinely collected microbiology and healthcare utilisation data covering all admissions to National Health Service (NHS) hospitals in Wales over a 2 year period.

Our aims were: (i) to illustrate the utility of a national microbiology dataset that can be linked to other routinely collected electronic health data; (ii) to quantify the proportion of emergency admissions for COPD undergoing testing for respiratory pathogens, and the proportion tested where viral or bacterial pathogens were identified; and (iii) to determine the accuracy of using ICD-10 diagnosis codes to identify laboratory-confirmed respiratory pathogens associated with COPD exacerbations.

Methods

We accessed complete coverage, person-level, anonymised datasets from the Secure Anonymised Information Linkage (SAIL) Databank,[17] which receives routinely collected data from all NHS hospitals in Wales, to examine all emergency hospital admissions due to COPD over a two-year period (1/12/2016 to 30/11/2018). This report of our findings was prepared according to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement.[18] The study was approved by the SAIL Information Governance Review Panel (project number 0996).

Data sources, population, and case definitions

Hospital admissions data were extracted from the Patient Episodes Database for Wales (PEDW), a dataset which includes diagnosis codes for all NHS hospital admissions in Wales. Emergency admissions for COPD were defined as those with an ICD-10 COPD code (J43, J44) recorded in the first or second position in any Finished Consultant Episode (FCE) in the population aged ≥35 at date of admission.

We defined two methods of classifying emergency COPD admissions as being associated with specific respiratory pathogens: (1) using pathogen-specific ICD-10 diagnosis codes (the full code set used is available in **supplementary material S1**), and (2) using microbiology test results. Microbiology data were extracted from the Welsh Results Reporting Service (WRRS), which receives results from all NHS hospital laboratories in Wales. Person-level linkage with hospital admissions data was possible using the Anonymised Linkage Field, which has been described previously.[19] We included individuals with high quality linkage (where there was either exact matching of NHS number or matching probability ≥ 90% (using name, sex, date of birth, postcode)). Laboratory diagnosis of respiratory viruses was all based on reverse transcription polymerase chain reaction (RT-PCR) and PCR testing, but it could not be established whether nasal or throat swabs were collected. Bacteria were detected by culture of sputum samples.

Pathogens of interest were influenza (A and B), respiratory syncytial virus (RSV), parainfluenza, rhinovirus, human metapneumovirus (hMPV), adenovirus, enterovirus, *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis* and *Pseudomonas aeruginosa*. The choice of respiratory viruses was dictated by those included on multiplex panels over the time period studied.

We used laboratory data to determine the proportion of COPD admissions where testing for bacterial and/or viral respiratory pathogens was conducted and estimated the proportion of COPD admissions with laboratory-confirmed infection (with the total number tested as our denominator). We defined admissions associated with laboratory-confirmed infection as those where the collection date of the specimen with a positive result was within (+/-) 7 days of hospital admission date. We assessed the seasonality of virus-associated admissions using methods adapted from Li et al,[20] where seasonality exists if at least 75% of the annual total of positive cases occur in ≤ 5 consecutive months in a year.

Accuracy of ICD-10 coding

Using COPD admissions associated with laboratory-confirmed infection as our reference standard, we assessed the accuracy of ICD-10 diagnosis codes in identifying respiratory pathogens associated with COPD admissions. Measures of accuracy were positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity, each with a 95% confidence interval. The sampling frame for these analyses was all COPD admissions where testing for the pathogen in question was conducted within (+/-) 7 days of admission. PPV was calculated as the proportion of COPD admissions with a pathogen-specific ICD-10 code that had a laboratory-confirmed respiratory pathogen on testing. NPV was calculated as the proportion of COPD admissions without a pathogen-specific ICD-10 code when there was a negative respiratory pathogen test. Sensitivity was calculated as the proportion of COPD admissions with a laboratory-confirmed respiratory pathogen that had a pathogen-specific ICD-10 code. Specificity was calculated as the proportion of COPD admissions with a negative respiratory pathogen test and without a pathogen-specific ICD-10 code.

Results

We analysed data from 15,950 people who had 25,715 emergency admissions for COPD over the two year period 1/12/2016 to 30/11/2018. Median age at admission was 73 (interquartile range 66–80). Emergency admissions for COPD were fewer over the summer months (Fig. 1), and peaked at a mean of 1,480 admissions in the month of January.

99.5% (25,596/25,715) of emergency COPD admissions could be linked to a laboratory record with a specimen collection date within (+/-) 7 days of the admission date. The proportion of admissions successfully linked to laboratory data was >99% in the majority of NHS Providers in Wales (**supplementary material S2**).

Respiratory pathogens associated with emergency COPD admissions: laboratory data

A specimen for sputum culture was collected in 5,013 (19.5%) out of 25,715 COPD admissions. Of those admissions where a sputum sample was collected, 1,232 (24.6%) were associated with

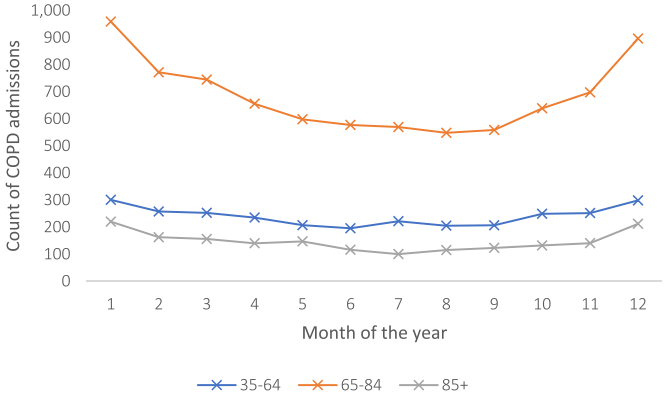

Fig. 1. Mean count of monthly emergency admissions for COPD in Wales, by age group.

Table 1
Respiratory pathogen testing and results for specimens associated with emergency admission for COPD.

Respiratory pathogen	Count of COPD admissions tested	Count of COPD admissions positive (percent positive*)
H.Influenzae	5,013	837 (16.7%)
S.Pneumoniae	5,013	154 (3.1%)
M.Catarrhalis	5,013	131 (2.6%)
P.Aeruginosa	5,013	200 (4.0%)
Influenza	1,219	262 (21.5%)
Rhinovirus	1,208	150 (12.4%)
RSV	1,214	83 (6.8%)
Parainfluenza	1,208	56 (4.6%)
hMPV	1,208	63 (5.2%)
Adenovirus	1,007	10 (1.0%)
Enterovirus	1,007	10 (1.0%)

* Percent positive = detected on laboratory test within 7 days of admission as a percentage of the total tested.

growth of one of the aforementioned bacteria. The most frequently observed bacteria was *H.influenzae,* which was cultured in 16.7% of admissions where a sputum sample was collected. The other bacteria under investigation all occurred at an overall percent positivity of <5% (Table 1).

A specimen for respiratory virus testing was collected in 1,219 (4.7%) of COPD admissions, and of those admissions associated with any respiratory virus testing, 569 (46.7%) returned any positive result. The most frequently detected virus was influenza, identified in 21.5% of admissions where testing was carried out, followed by rhinovirus (12.4%), RSV (6.8%) and hMPV (5.2%).

Of the 491 admissions where both sputum collection and viral testing was carried out, 41 (8%) admissions were associated with both bacterial growth in sputum and a positive respiratory virus test.

Testing frequency and percent positive rate varied by pathogen (Table 1), with sputum collection more frequent than viral testing, and the highest percent positive levels seen for influenza, rhinovirus and *H.influenzae.* There was also marked variation in testing frequency and percent positivity by month of admission for the viral pathogens, with influenza percent positivity ranging from 0% in the UK summer months, to > 30% in January and February (Table 2). Over 75% of the total influenza-associated COPD admissions occurred over the UK winter months (December, January, February). RSV and hMPV-associated COPD admissions also showed seasonality (>75% of total admissions occurring over November to January for RSV, and December to March for hMPV), in contrast to admissions associated with rhinovirus, parainfluenza, and the bacterial pathogens. Counts of positive adenovirus and enterovirus tests were small, and thus not analysed by month.

Accuracy of ICD-10 diagnosis codes in detecting respiratory pathogens associated with emergency COPD admissions

The ICD-10 diagnosis codes used to identify influenza-associated COPD admissions performed best in our data, compared to those used for other pathogens, with a sensitivity of 59.2% (95% confidence interval 52.9–65.1%), PPV of 86.1% (80.6–90.2%), NPV of 89.7% (88.3–91.0%) and specificity of 97.4% (96.2–98.3%) (Table 3).

Sensitivities of the ICD-10 codes related to the other respiratory pathogens were substantially lower, although those of the bacteria were generally higher than the non-influenza viruses (**supplementary material S3**). *P.aeruginosa* ICD-10 codes had the highest sensitivity of all the non-influenza pathogens (42.5% (95% CI 35.6–49.7%), but also had a lower PPV (48.0% (41.6–54.5%)), compared to a PPV >80% for all other pathogens where PPV can be reported;

Table 2
Respiratory pathogen testing, results and percent positive rate for specimens associated with emergency admission for COPD, by month of admission (1/12/2016 to 30/11/2018 data combined).

Month of admission with COPD	Influenza (percent positive*)	Rhinovirus	RSV	Parainfluenza	hMPV	HINF	SPNE	MCAT	PAER
January	109/338 (32.2%)	30/333 (9.0%)	29/333 (8.7%)	6/333 (1.8%)	21/333 (6.3%)	119/578 (20.6%)	19/578 (3.3%)	16/578 (2.8%)	16/578 (2.8%)
February	70/202 (34.7%)	14/202 (6.9%)	5/202 (2.5%)	<5/202 (0.5–1.0%)	8/202 (3.9%)	82/491 (16.7%)	15/491 (3.1%)	7/491 (1.4%)	15/491 (3.1%)
March	32/122 (26.2%)	11/122 (9.0%)	<5/122 (0.8–3.3%)	<5/122 (0.8–3.3%)	5/122 (4.1%)	77/440 (17.5%)	15/440 (3.4%)	11/440 (2.5%)	15/440 (3.4%)
April	11/72 (15.2%)	14/72 (19.4%)	<5/72 (1.4–5.6%)	14/72 (19.4%)	<5/72 (1.4–5.6%)	73/405 (18.0%)	10/405 (2.5%)	13/405 (3.2%)	13/405 (3.2%)
May	<5/49 (2.0–8.2%)	5/49 (10.2%)	0/49	<5/49 (2.0–8.1%)	<5/49 (2.0–8.1%)	61/376 (16.2%)	10/376 (2.7%)	11/376 (2.9%)	13/376 (3.5%)
June	0/42	7/42 (16.7%)	0/42	5/42 (11.9%)	<5/42 (2.4–9.5%)	50/358 (14.0%)	10/358 (2.8%)	5/358 (1.4%)	20/358 (5.6%)
July	0/29	<5/29 (3.4–13.8%)	0/29	<5/29 (3.4–13.8%)	<5/29 (3.4–13.8%)	66/334 (19.8%)	5/334 (1.5%)	7/334 (2.1%)	14/334 (4.2%)
August	0/23	5/23 (21.7%)	0/23	<5/23 (4.3–17.4%)	<5/23 (4.3–17.4%)	50/307 (16.3%)	6/307 (2.0%)	7/307 (1.0%)	19/307 (5.8%)
September	0/31	10/31 (32.3%)	<5/31 (3.2–12.9%)	<5/31 (3.2–12.9%)	<5/31 (3.2–12.9%)	53/344 (15.4%)	8/344 (2.3%)	6/344 (1.7%)	22/344 (6.4%)
October	<5/71 (1.4–5.6%)	22/69 (31.9%)	<5/71 (1.4–5.6%)	5/69 (7.2%)	<5/69 (1.4–5.8%)	66/394 (16.8%)	8/394 (2.0%)	9/394 (2.3%)	17/394 (4.3%)
November	<5/86 (1.2–4.7%)	8/82 (9.8%)	9/86 (10.5%)	<5/82 (1.2–4.9%)	<5/82 (1.2–4.9%)	63/471 (13.4%)	21/471 (4.5%)	19/471 (4.0%)	22/471 (4.7%)
December	30/154 (19.5%)	20/154 (13.0%)	32/154 (20.8%)	7/154 (4.5%)	14/154 (9.1%)	87/515 (16.9%)	27/515 (5.2%)	20/515 (3.9%)	14/515 (2.7%)

Small counts have been masked as <5.
HINF = *H.Influenzae*, SPNE = *S.Pneumoniae*, MCAT = *M.Catarrhalis*, PAER = *P.Aeruginosa*
* Percent positive = detected on laboratory test within 7 days of admission as a percentage of the total tested

Table 3
Contingency table showing accuracy of influenza ICD-10 codes associated with emergency admission for COPD, as compared to laboratory test result.

	Laboratory test		
Diagnosis	Positive	Negative	Total
ICD-10 code present	155	25	180
ICD-10 code absent	107	932	1039
Total	262	957	1,219

Sensitivity = 59.2% (52.9–65.1%); Specificity = 97.4% (96.2–98.3%); PPV = 86.1% (80.6–90.2%); NPV = 89.7% (88.3–91.0%).

Table 4
Contingency table showing accuracy of *P.aeruginosa* ICD-10 codes associated with emergency admission for COPD, as compared to laboratory test result.

	Laboratory test		
Diagnosis	Positive	Negative	Total
ICD-10 code present	85	92	177
ICD-10 code absent	115	4,721	4836
Total	200	4,813	5,013

Sensitivity = 42.5% (35.6–49.7%); Specificity = 98.1% (97.7–98.5%); PPV = 48.0% (41.6–54.5%); NPV = 97.6% (97.3–97.9%).

Table 4). Specificities were high (>95%) for all pathogens where this can be reported.

Due to low counts in the contingency tables for parainfluenza and hMPV, all accuracy measures cannot be reported for these pathogens, but sensitivities were <8.9% (parainfluenza) and <7.9% (hMPV). *M.catarrhalis* is not associated with any pathogen-specific ICD-10 codes, and so could not be included in these analyses.

Discussion

Our national level analyses of microbiology testing related to emergency COPD admissions in Wales reveals widespread underutilisation of diagnostic microbiology for severe AECOPD, and a high percent positivity for respiratory viruses, with 46.7% of admissions in which testing was carried out returning a positive result. Given the frequency with which AECOPD admissions occur, the prevalent use of antibiotics for this presentation, and the growing problem of antimicrobial resistance, our data suggests that more widespread use of viral testing could be beneficial in advancing antibiotic stewardship. In addition, increased viral testing would enable timely isolation of cases in healthcare settings in order to reduce transmission to other, often vulnerable, hospital inpatients.

We demonstrate how using ICD-10 diagnosis codes to detect respiratory pathogens associated with COPD admissions in our study would have considerably underestimated the burden of these infections. Researchers using ICD-10 codes as substitutes for raw microbiology data should be aware that coding deficiencies may lead to a substantial loss in accuracy.

Furthermore, our study illustrates the feasibility and utility of linking national microbiology data with other routinely collected electronic health data, which has innumerable potential applications in future research.

The strengths of our study include the complete population coverage, with a base dataset covering all admissions to hospitals in Wales, and the high level (99.5%) of successful linkage between hospital admissions and microbiology data. This was possible due to the recent development of a national system in Wales, the Wales Results Reporting System, which has brought together the results of all laboratory investigations from all providers, whether instituted in community or hospital settings. Whilst there are linkages in individual hospital based systems in the UK, there is no other system that links laboratory results to other routinely collected health data at a national population level. This system has allowed us to gain insight into real-world patterns of microbiology testing in emergency admissions with COPD, estimate the contribution of bacterial and viral pathogens to severe AECOPD, and report the accuracy of pathogen-specific ICD-10 diagnosis codes.

Our study has some limitations. People undergoing microbiology tests may be those whom clinicians consider most likely to have an infective aetiology of their AECOPD, therefore extrapolating the proportion of positive tests to the total number of AECOPD hospitalisations would likely be an overestimate. Nevertheless, the majority of AECOPD are thought to be infective in nature,[1] the proportion of our admissions associated with respiratory viruses was consistent with previous studies,[21,22] and the high percent positivity rate suggests a large number who were not tested would also test positive. Patterns of respiratory virus transmission change year to year, and the winter of 2017/2018 saw a high level of influenza in the UK. We were confined to analysing a 2 year period due to data availability, so how representative our data is of other years is uncertain, though general patterns are likely to remain consistent. Co-infection between respiratory viruses and bacteria may be underestimated in our data, since some pathogens were not tested for or not included in our study, such as the seasonal coronaviruses. We have not reported subtypes of the respiratory viruses such as influenza or parainfluenza due to paucity of data in this regard. Lastly, the role of microorganisms in the aetiology of AECOPD has previously been unclear due to potential contamination of sputum samples by the upper airway, chronic bacterial colonisation that can occur in the lower airways of those with COPD, a lack of definitive improvement in AECOPDs treated with antibiotics in randomised controlled trials,[23] and studies reporting asymptomatic detection of rhinovirus.[24] However, studies demonstrating the development of specific immune responses to bacteria after exacerbations support the causative role of bacteria in the exacerbation,[25,26] trials may have been weakened due to inclusion of AECOPD with non-bacterial aetiology, and respiratory viruses aside from rhinovirus are not commonly identified in stable disease.[24] Nevertheless, we are unable to infer from our data that any microorganisms detected directly contributed to development of the COPD exacerbation.

In the context of other research, prospective studies[27–33] have provided useful estimates of pathogen distribution in AECOPD due to avoidance of selective testing strategies. However, due to the expense involved with such study designs, they are mostly limited to small, selected populations or regions. Our results broadly reflect those previously published. For example, in Brendish et al's prospective study,[34] 42% of patients presenting to hospital with an exacerbation of their airways disease tested positive for respiratory viruses, compared to 46.7% in our data. Others have also demonstrated increased percent positivity of respiratory viruses in COPD admissions during winter months.[28]

Data from a randomised controlled trial has shown that point-of-care testing (POCT) for influenza can allow timely treatment with antivirals and swift isolation in healthcare settings, minimising nosocomial spread to frail populations.[35] Another study demonstrates increased early discontinuation of antibiotics in those with underlying airways disease testing positive for a respiratory virus on POCT.[34]

Evidence of the importance of the non-influenza respiratory viruses on the adult population has grown in recent years. RSV has been shown to be associated with 11% of COPD hospitalisations in a prospective US-based study,[36] and >900,000 inappropriate antibiotic prescriptions each season in a UK-based modelling study.[37] With progress in the development of vaccination against RSV,[38] further data regarding the burden of RSV-associated disease by age, geography, and comorbidity is key to guide future vaccination strategy,[39] and our data contributes to this. With regard to previous research examining routinely collected microbiology data,

other studies have also identified underutilisation of diagnostic microbiology testing[40] and low sensitivity of ICD codes to identify laboratory-confirmed non-influenza respiratory infection.[41,42]

To summarise, our findings of a high percent positivity of respiratory viruses amongst those hospitalised with AECOPD, low utilisation of microbiology testing, and limitations of ICD-10 codes in identifying the burden of respiratory infections generate several key targets for further work. These include increasing the use of diagnostic testing in AECOPD, along with translation of this into reduced antimicrobial prescribing and timely infection control measures, and increasing the ability to perform linkage of existing electronic health databases to routinely collected microbiology data, which would have almost countless future applications.

Data availability

The anonymised person-level data used in this study are held by the SAIL Databank and not publicly available. All proposals to use the SAIL Databank are carefully reviewed by an independent Information Governance Review Panel to ensure proper and appropriate use of data (https://www.saildatabank.com/application-process). When approved, access is then provided through the SAIL Gateway, a privacy-protecting safe haven and a secure remote access system.

Contributors

SS conceived the study in collaboration with all authors, conducted the analysis with advice from MA, and drafted the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Ethics

We were granted permissions from SAIL's independent Information Governance Review Panel to conduct this study. Ethical review was not required as only anonymised data were used.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.012.

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