Use of routinely collected electronic health record data to predict anti-microbial resistance in chronic *P. aeruginosa* lung infection

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Background

Pseudomonas aeruginosa is a World Health Organisation Priority 1 pathogen and is a major cause for healthcare-associated infections worldwide.[1] *P. aeruginosa* has high levels of intrinsic resistance to antibiotics as well as an ability to rapidly evolve resistance. In adulthood, nearly half of adults living with cystic fibrosis **(CF)** are chronically infected with *P. aeruginosa* and acute exacerbations of pulmonary disease are often treated with extended courses of dual intravenous anti-pseudomonal antibiotics.[2] As such, as lung disease progresses, increasing use of antibiotics is needed and antimicrobial resistance **(AMR)** often develops.

Evidence for specific antibiotic regimens, combinations or durations is limited in the CF setting and similarly, very little is known about the relative cumulative contributions of individual agents/regimens to long-term AMR trajectories for people living with CF. At present, antibiotic regimen/agent selection is largely empirical, but machine learning applied to large datasets of routinely collected healthcare data can in theory potentially facilitate more precise approaches to antibiotic selection in chronic lung infection.

Liverpool Heart & Chest Hospital NHS Foundation Trust **(LHCH)** is home to a large regional tertiary adult CF centre and switched to fully integrated electronic health record **(EHR)** in 2013. As such, the adult CF centre now has a mature EHR with routinely collected and maintained databases consisting of antibiotic usage records, sputum cultures, antibiotic susceptibilities and clinical outcomes stretching back a decade. This large database with standardised longitudinal data capture provides an excellent resource to adopt machine learning techniques to improve understanding and predict the complex relationship between antibiotic usage and AMR development in people living with CF. In particular, using historical usage data to predict the presence of AMR may ultimately lead to the ability to initiate more optimal regimens at outset of treatment, thereby simultaneously improving clinical outcomes and antibiotic stewardship.

Aims

This study aims to explore the ability of machine learning to predict AMR profiles

Methods:

Data source:

The LHCH adult CF centre looks after approximately 350 adults with cystic fibrosis. The EHR (AllScripts, Altera Digital Health) at LHCH has been in place for approximately 10 years and includes comprehensive prescribing data, clinical outcome data and microbiological data. While the data sources differ, the integrated system allows a single point of access. All adults with CF at LHCH are consented into the the national UK CF Registry which involves annual upload of centre-level and patient specific data. Data extraction from aggregate data compiled for these uploads was conducted by the routine clinical care team. In addition, the CF centre maintains a rolling record of intravenous antibiotic usage. For the purposes of this study, routinely collected aggregated data was completely anonymized by the clinical care team to allow use for research purposes.

Data was comprised of two main bodies of data. First, microbiology results data consisting of sputum microbiology for all adults with CF attending LHCH from 2012-2022. These data include organisms cultured and antimicrobial resistance profiles. Second, admission data with each prescription of intravenous antibiotics prescribed during an admission were obtained.

Data Description:

The number of times each antibiotic was administered to a patient in the previous six and twenty-four months was extracted from the admission data with intravenous antibiotic prescriptions in order to improve the Microbiology Results dataset. The cumulative count of antibiotic doses for each patient over the specified periods was computed to acquire this data. This merging process creates a comprehensive dataset containing both microbiology profiles and antibiotic usage history for each patient.

The resulting dataset, which includes both microbiology data and cumulative antibiotic usage, was used as the final training dataset. It served as the input to train a machine learning (ML) model for predicting multidrug resistance (MDR) cases among adults with CF at LHCH and individual resistance.

The input features were pre-processed and normalised in order to guarantee numerical stability before being used for training an ML model. The data were split into training (80%) and test set (20%), so that the model performance can be appropriately evaluated on an independent test set (unseen by the model during the training). This resulted in 13,440 observations used for training and 3,360 as an independent test set.

Machine Learning model development:

For the development of the ML model, we used Long Short-term Memory (LSTM), which is a type of recurrent neural network architecture designed to handle sequences and time-series data. LSTM has memory cells with self-loop connections that allow them to retain information over extended periods, making them capable of learning and capturing long-term dependencies in sequential data. This enables LSTM to model and predict sequences effectively, making it widely used in tasks such as time-series analysis.

Developing an optimal LSTM model requires the tuning of its hyperparameters. Hyperparameters such as the number of LSTM units, batch size, learning rate, and dropout rate were fine-tuned to improve the model's accuracy and generalization. Techniques like cross-validation were employed to assess model performance under different hyperparameter configurations. The specific hyperparameters used in the final model were based on the results obtained during this tuning process.

The final LSTM model was developed with the following architecture:

- Conv1D layer with 80 filters and kernel size of 3, followed by MaxPooling1D with pool size 2.
- Another Conv1D layer with 64 filters and kernel size of 3, followed by another MaxPooling1D with pool size of 2.
- LSTM layer with 64 units.
- Dropout layer with a dropout rate of 0.2 to mitigate overfitting.
- Dense layer with a sigmoid activation function to produce the final binary classification output.
- The model was compiled using binary cross-entropy loss and the RMSprop optimizer. The accuracy metric was used to evaluate the model's performance during training.

The model was trained using the training data, with a batch size of 64 and validation split of 0.2 to monitor the performance on the validation set during training. The training was stopped early using Early Stopping when no improvement in accuracy was observed.

The LSTM model's last layer had a sigmoid activation function set up, which converted model outputs to a probability ranging from 0 to 1. These probabilities were turned into binary forecasts (MDR or non-MDR). Youden's J Statistic was used separately for each antibiotic model and for predicting the multi-resistance output in order to determine the best threshold that strikes a balance between precision and recall. For each antibiotic model, the threshold value that maximised the Youden's J Statistic was determined for a range of threshold values. The best performance for each antibiotic was obtained at the optimal threshold that was selected. While reducing false positives and false negatives for that output. The Youden's J Statistic thresholds were chosen as the best options for producing binary predictions for each antibiotic, and they were used in the final model to produce the best results.

Results:

In total, 16,800 sputum samples and 8401 antibiotic prescriptions were available from 284 people living with cystic fibrosis. Mean age was 25.2 years, 148/284 (52.1%) were male. A wide range of organisms were identified with *P. aeruginosa* followed by *Staphylococcus aureus* the most common. 10,561 were positive for *P. aeruginosa* and resistance profiles are set out in **Table 1**. Co-ocurrence of resistance is set out in **Figure 1**, where fully sensitive *P. aeruginosa* was the most prevalent resistance pattern, but resistance to ciprofloxacin, ceftazidime, meropenem and piperacillin/tazobactam was the second most prevalent profile and ciprofloxacin monoresistance was the third most prevalent profile.

Table 1: Resistance profiles for sputum cultures positive for Pseudomonas aeruginosa

Antimicrobial	Total samples tested	Resistant	%
Ciprofloxacin	10476	5668	54.10
Ceftazidime	10511	5615	53.42
Meropenem	10507	4514	42.96
Piperacillin/Tazobactam	10500	3042	28.97
Tobramycin	7737	356	4.60

Multi-drug resistance (MDR) was defined as resistance to 3 or more antibiotic agents and was present in 3846/10561 (28.8%) of samples, see **Figure 2.** The most prevalent MDR profile was resistance to ciprofloxacin, ceftazidime, meropenem, piperacillin/tazobactam but sensitivity to tobramycin. The second most prevalent MDR profile was resistance to ceftazidime, meropenem, piperacillin/tazobactam but sensitivity to ciprofloxacin and tobramycin. Only 23/10561 (0.2%) were resistant to all five agents. IV antibiotic usage is presented in **Figure 4**, with tobramycin and meropenem the most frequently used agents.

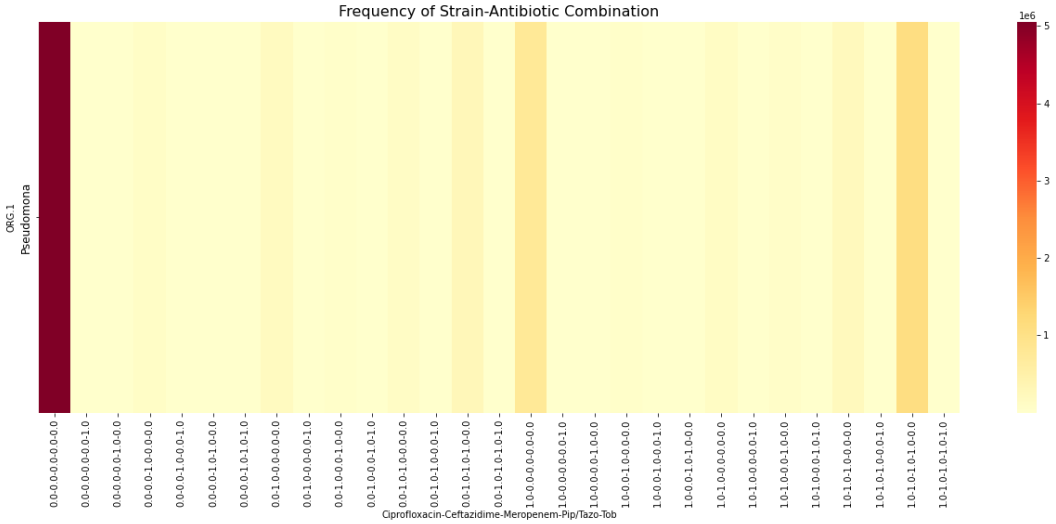

Figure 1: Co-occurrence of antibiotic resistance in sputum cultures positive for *P. aeruginosa*. Resistance is indicated in the x-axis (1.0=Resistant, 0.0=Non-resistance.)

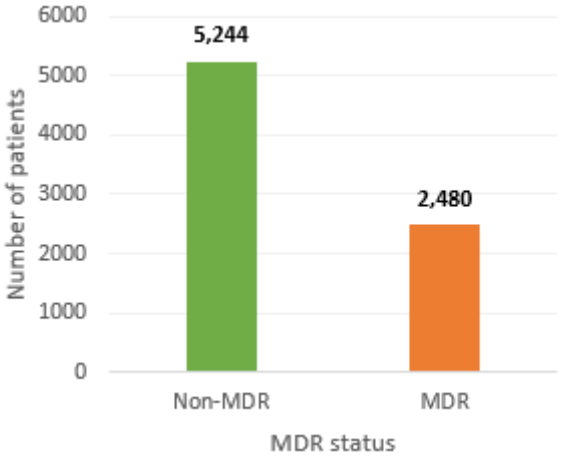

Figure 2: Distribution of multi-drug resistance (MDR) status in sputum samples positive for *P. aeruginosa*

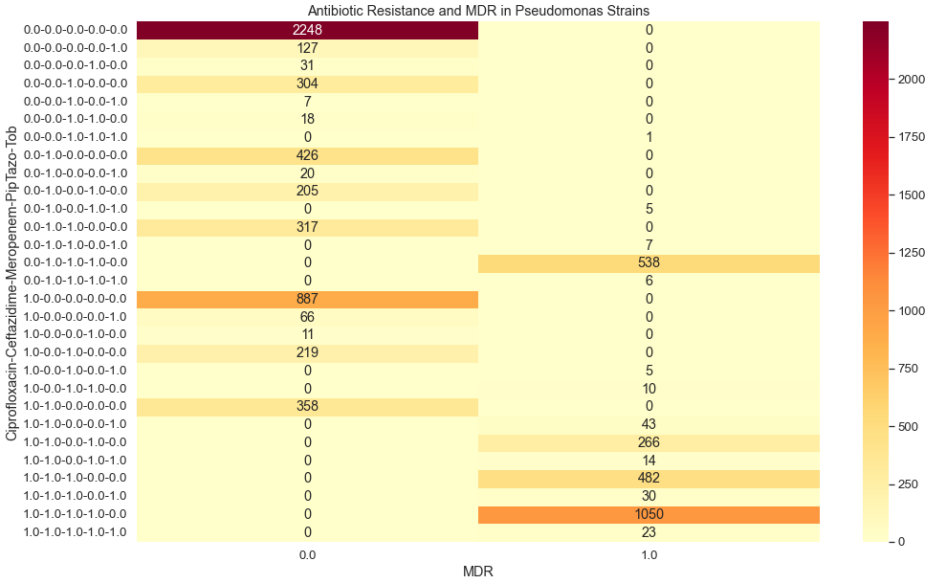

Figure 3: Co-occurrence of multi-drug resistance (MDR) in sputum cultures positive for *P. aeruginosa*

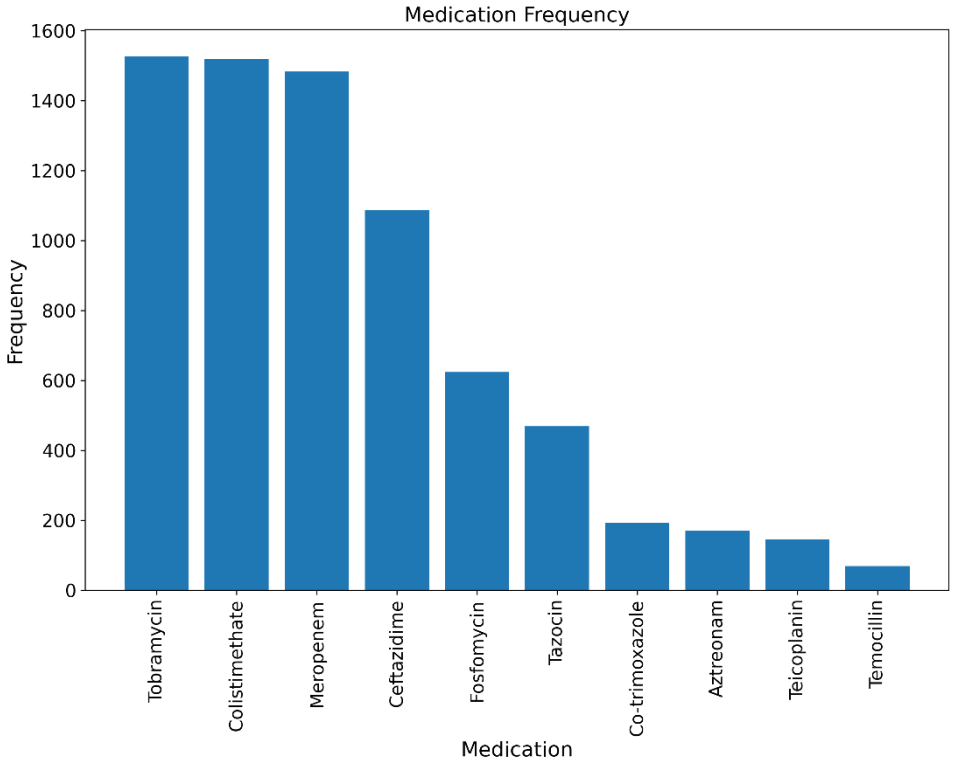

Figure 4: Antibiotic usage over the study periods. Frequency relates to total number of days each antibiotic was prescribed for in the study period

"Last result carried forward" prediction of multi drug resistance

Multi-drug resistance is a varying phenotype in the sputum of people living with cystic fibrosis. To illustrate this we calculated the predictive power of just using the previous sample from an individual to predict the presence of multi-drug resistance in the subsequent sputum sample, i.e. "last result carried forward". Of 3846 samples which were MDR, 1731 were also MDR on the preceding sputum sample. Of those 6707 samples not MDR, 3565 were also not MDR on the preceding sample. Overall, this gives a sensitivity of 45.1% and a specificity of 53.2%

Machine learning prediction of multi-drug resistance

Model performance for the ability to detect multidrug resistance is presented in **Table 2**. Overall the model showed excellent performance with an area under the curve (AUC) of 0.997 and F1 score of 0.970.

Table 2: Model performance for the prediction of multi-drug resistance (MDR) in sputum samples positive for *P. aeruginosa*

	AUC	Accuracy	Precision	Sensitivity (recall)	Specificity	F1-score
MDR	0.997	0.986	0.950	0.992	0.984	0.971

Machine learning prediction of individual antibiotic resistance

Model performance for the ability to detect resistance to individual antibiotic agents is presented in **Table 3.** For meropenem, piperacillin/tazobactam and ceftazidime the models showed excellent discriminatory ability with AUC of >0.9 and good F1-scores of >0.8.

Table 3: Model performance metrics for the prediction of individual antimicrobial resistance in the

	AUC	Accuracy	Precision	Sensitivity (recall)	Specificity	F1-score
Tobramycin	0.861	0.945	0.193	0.808	0.748	0.312
Meropenem	0.830	0.740	0.710	0.692	0.777	0.701
Piperacillin Tazobactam	0.961	0.913	0.725	0.928	0.909	0.814
Ciprofloxacin	0.831	0.748	0.775	0.602	0.862	0.678
Ceftazidime	0.914	0.881	0.943	0.739	0.972	0.829

Model performance was noticeably diminished for predicting tobramycin resistance (AUC 0.86, F1-score 0.42) and ciprofloxacin resistance (AUC 0.83, F1-score 0.66).

DISCUSSION:

In this study, which is the first to test the ability of machine learning to predict antimicrobial resistance in cystic fibrosis, we developed an LSTM model with excellent performance for predicting

the presence of MDR *P. aeruginosa.* Similar models predicted individual antibiotic resistance to a more variable but still extremely credible extent.

The models used here incorporate simple and readily available data mined from electronic healthcare records consisting of previous sputum culture results, linked antimicrobial resistance profiles and historical antibiotic usage data. The combination of these inputs into machine learning models resulted in dramatic improvement in predictive performance when comparing against the "last result carried forward" approach often routinely used in clinical practice. For example in MDR *P. aeruginosa,* sensitivities of 98.7% vs 48.5% and specificities of 99% vs 53.2% were seen for LSTM model and the "last result carried forward" method respectively.

This finding is of high clinical relevance given it often takes 48-96 hours to get a full antimicrobial resistance profile from a fresh sputum sample. Treatment decisions at the time of acute pulmonary exacerbation include whether to start antibiotics and if so, which antibiotic agent and at what dose. Antibiotics agent and dose are often dictated by the clinician's perception of risk of AMR in that individual. Our data suggests that taking the previous sputum sample alone to assess risk of AMR is often no better than tossing a coin for predicting multi drug resistance in people living with CF and chronic *P. aeruginosa* infection, however our models incorporating huge numbers of historical results as well as individualised antibiotic usage data dramatically improved predictive performance. These models could, in an optimised setting, be available to the clinician at the time of antibiotic prescription, up to 96 hours sooner than conventional culture results. Such information could optimise clinical outcomes while also mitigating the development of antimicrobial resistance.

For individual antibiotic resistance prediction, the models performed less well for tobramycin and ciprofloxacin. A potential explanation for this is that tobramycin resistance was highly imbalanced with <10% of samples resistant, perhaps limiting the power to detect and predict resistance. However, this feature does not explain the ciprofloxacin performance, given ciprofloxacin resistance is much more balanced with an almost 50:50 split between resistance and non-resistance. A different explanation is that tobramycin and ciprofloxacin are the only agents used frequently in non-intravenous settings. For example, ciprofloxacin is used frequently as first line oral treatment for mild-moderate exacerbations of CF and tobramycin is used frequently in the chronic suppression of *P. aeruginosa* via inhaled formulations.[3] Extra utilisation of these agents outside of the dataset would likely induce resistance but would not be predictable by the inputs available to us from this data. Inhaled antibiotic prescriptions are centrally commissioned and form part of the "banding" funding received by CF centres so that data is also readily available and should be explored in future studies.[4]

<u>Limitations:</u>

The limitations to this work include the retrospective, single-centre nature of the study and further work is needed to expand, improve and validate this work prospectively. Similarly, the relationship between AMR and clinical outcomes is unclear in cystic fibrosis. For example, a systematic review by the AMR in CF International Working Group found only 2 of 11 studies reported AMR at baseline was linked to treatment outcomes. Our data supports this given the highly variable nature of MDR profiles over time and poor predictive ability for subsequent MDR profiles. It is not clear from the included studies whether the baseline resistance was known prior or subsequent to treatment initiation, but our data highlights the need for more research in this area.

<u>Further work and potential impact:</u>

This work will be prepared for submission to the European Respiratory Society Congress 2024 and European Congress of Clinical Microbiology and Infectious Diseases 2024. A manuscript is being prepared for submission to peer-reviewed journals.

This proof-of-concept work will directly inform further grant applications to expand this approach. Possible avenues include expansion of this project within CF by seeking external partners allowing robust external validation. Further work is needed to understand the relative contribution and importance of each model input such that appropriate candidate inputs can be identified in other datasets. Additionally, within the scope of this project we were only able to crudely include cumulative antibiotic usage within a certain time-frame. Sensitivity analyses comparing the time-frame thresholds and also expanded techniques allowing full appreciation of usage patterns may shed further insight and improvement performance and therefore need to evaluated.

There is huge scope for this approach to be applied to much larger disease areas such as COPD and bronchiectasis using potentially massive datasets e.g. primary care or city-wide microbiological data. Ultimately, implementation would allow personalised antibiotic choices at the time of exacerbation with the potential to optimise clinical outcomes, minimise treatment failure and mitigate antimicrobial resistance at scale.

Conclusion:

In this study we provide proof-of-concept for machine learning approaches to reliably predict antimicrobial resistance in sputum samples positive for *P. aeruginosa* in people living with CF. Further work is needed to refine, externally validate and expand this research to pave the way for optimal clinical implementation and impact.

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