

# Artificial Intelligence-Driven Clinical Decision Support for Antibiotic Optimisation

William Bolton

Viva

10<sup>th</sup> February 2025



Contents.









Imperial College London Antimicrobial resistance is a global threat with data driven approaches towards stewardship neglected.

**CO-MORBIDITIES** 

Antimicrobial resistance is a • growing global threat. One key strategy to tackle this is to optimise antimicrobial use

MOTIVATION

- AI clinical decision support systems have been developed to support infection management
- However antimicrobial stewardship has been **neglected**
- The uptake and utilisation of such systems have been limited to date, in part due to integration and behavioural issues.



IV TO PO



Imperial College addressed my PhD hypothesis through three overarching themes.

**CO-MORBIDITIES** 

# Hypothesis:

Artificial intelligence-based clinical decision support systems utilising routinely collected electronic health record data can support antibiotic stewardship

IV TO PO

Chapter 3

Co-morbidity Representation in AI

MOTIVATION

London

Chapter 4 Antibiotic Cessation Decision Support

Create methods to appropriately represent routinely collected patient data

Chapter 4 Antibiotic Cessation Decision Support

Chapter 5	
ntravenous to Oral Switch Decision Support	t

Develop novel decision support systems

Chapter 6

2.4 Moral AI for antimicrobial resistance

**FUTURE WORK** 

Clinician Evaluation

Understand the ethical, and behavioral components of decision making



Imperial College London Using AI to optimise antimicrobial prescribing raises important ethical questions.

IV TO PO

1

**CO-MORBIDITIES** 

How can a **moral balance** be obtained between the needs of an individual patient and those of wider and future society?

MOTIVATION

**ETHICS** 

Variables	Description	Exemplar of starting antimicrobial treatment	Corresponding ad-hoc utility value	
Intensity	How strong is the pleasure?	Treating a relevant infection with antimicrobials has the potential to save that person's life		
Duration	How long will the pleasure last?	Any extension of life is immeasurable while it is reasonable AMR will continue in the near-term future	Positive utility	
Certainty or uncertainty	How likely or unlikely is it that the pleasure will occur?	Limited information often means treatment may or may not be helpful and there is always an inherent risk of developing AMR	Neutral utility, without more information	
Propinquity	How soon will the pleasure occur?	Treatment can be effective immediately however the same is true for the evolution of AMR	Neutral utility, without more information	
Fecundity	The likelihood of further sensations of the same kind	-	Unable to assign	
Purity	The likelihood of not being followed by opposite sensations	-	Unable to assign	
Extent	How many people will be affected?	Prescribing antimicrobials effects the patient and those close to them, while the development of AMR is a certainty and may affect everyone, causing significant suffering and mortality	Immense negative utility	

**CLINICIAN EVAL** 

**FUTURE WORK** 



Imperial CollegeMOTIVATIONETHICSCO-MORBIDITIESCESSATIONIV TO POCLINICIAN EVALFUTURE WORKEthical frameworks can help ensure Al systems are fair<br/>and moral.

## FINDINGS

- A **utilitarian approach** may be most suitable for developing AI-based CDSSs for AMR, given the potential **number of people affected** and **aligned aims** of extending life and providing equality
- Spatial and temporal considerations and heterogeneity are critical for infections diseases
- Aspects of AI such as **accountability, interpretability, and biases**, require further research
- We have a **responsibility** towards the health of future generations



Applied ethical theories to the nuanced problem of optimised antimicrobial prescribing through AI to tackle AMR





Imperial CollegeMOTIVATIONETHICSCO-MORBIDITIESCESSATIONIV TO POCLINICIAN EVALFUTURE WOCondonCO-morbidities are a problem for healthcare and AlSystems and increase an individual's risk of infection.



Co-morbidities or chronic long-term medical conditions increase infection risk and are a **major challenge in healthcare** 



Challenges such as combinatorial complexity, heterogeneity, and a lack of data make using disease data in AI systems difficult



We created meaningful embeddings from external medical knowledge, to help overcome these challenges



antimicrobic

optimisation

#### Imperial College London **CO-MORBIDITIES CLINICIAN EVAL** MOTIVATION IV TO PO Medical knowledge can help create informative disease and patent embeddings.

**FUTURE WORK** 



NHS Imperial College Healthcare

**NHS Trust** 





2,133 chronic conditions

Table 2: Mean results for the similar patient retrieval task.							
Method	SNOMED similarity score	Charlson Jaccard index					
One hot encodings	4.40 (SD 2.32)	0.88 (SD 0.30)					
Rocheteau's method	3.52 (SD 3.26)	0.69 (SD 0.20)					
Co-morbid patient embeddings	1.78 (SD 1.90)	0.84 (SD 0.34)					

Co-morbidities

Question 8 patient	Gestational diabetes mellitus	Hypertensive disorder	Pre- eclampsia	Varicella
Co-morbid patient embeddings	Gestational diabetes mellitus	Pregnancy- induced hypertension	Pre- eclampsia	Varicella
Rocheteau score	Gestational diabetes mellitus	Hypertensive disorder	-	Varicella
One hot encodings	Gestational diabetes mellitus	-	Pre- eclampsia	Varicella

**Contributions** 

CONCLUSION

Developed a **novel** generalisable pipeline to extract and utilize medical knowledge to **represent** diseases and co-morbid patients and demonstrated its utility in multiple tasks





# Imperial College MOTIVATION ETHICS CO-MORBIDITIES CESSATION IV TO PO CLINICIAN EVAL London Understanding antibiotic cessation with artificial intelligence.



Understanding when it is appropriate to **stop antibiotic treatment** is complex

Currently treatment durations are often decided based on habit or limited historical population evidence, with **extended durations common**  AUTOENCODER TRAINING

SYNTHETIC OUTCOME ESTIMATION

**FUTURE WORK** 







Use artificial intelligence to estimate the **impact of stopping antimicrobial treatment** on a patient's treatment response or outcome. Important factors influence cessation decision making



MOTIVATION

IV TO PO

CONCLUSION

no

# Imperial College Machine learning and synthetic outcome estimation for individualised antimicrobial cessation.

# AUTOENCODER PREDICTIONS

	Metric	Result
Martality Classification	AUROC	0.77
	Accuracy	0.73
LOS Regression	RMSE	3.88

## SYNTHETIC OUTCOME ESTIMATION

			LC	DS	Mortality				
SCENARIO	DAY(S)	Mean delta (days, p- value)	MAPE	MAE	RMSE	Mean delta	MAE	AUROC	
STOP	IMPACT	2.71*, <0.01	0.36	3.30	4.80	0.06	0.25	0.66	
	CONTROL	0.24, 0.60	0.26	1.32	1.93	0.05	0.15	0.72	
CONTINUE	IMPACT	-2.09*, <0.01	0.77	2.85	3.16	0.05	0.18	0.67	
CONTINUE	CONTROL	0.42*, 0.01	0.48	2.72	3.76	0.07	0.24	0.64	

### **Contributions**

Created a **novel bi**directional LSTM autoencoder model to estimate patient outcomes and treatment response under the **contrasting** scenarios of stopping or continuing antibiotic treatment





Imperial CollegeMOTIVATIONETHICSCO-MORBIDITIESCESSATIONIV TO POCLINICIAN EVALLondonSwitching from IV-to-oral antibiotic treatment is<br/>complex and under-researched.Complex and under-researched.



One key challenge of stewardship is **determining when to switch** antibiotics from **IV-to-oral administration** 

Oral therapy can be **non-inferior** to IV but there is a **poor understanding** of the factors that facilitate or inhibit an individual from receiving oral therapy





CONCLUSION

**FUTURE WORK** 

IV TO PO

**CLINICIAN EVAL** 

CONCLUSION **FUTURE WORK** 

Imperial College London Models achieve generalisable performance across a range of datasets and patient populations.

**CO-MORBIDITIES** 

	Metric	1 <sup>s⊤</sup> threshold results	2 <sup>nd</sup> threshold results	IVOS criteria baseline
MIMIC	AUROC	0.78 (SD 0.02)	0.69 (SD 0.03)	0.66
	FPR	0.25 (SD 0.02)	<b>0.10</b> (SD 0.02)	0.43
	Metric	1 <sup>st</sup> threshold results	2 <sup>nd</sup> threshold results	IVOS criteria baseline
elCU	AUROC	0.72 (SD 0.02)	0.65 (SD 0.05)	0.55
	FPR	0.24 (SD 0.04)	0.05 (SD 0.02)	0.28
		1		I
	Metric	Initial Results	Prospective dataset	Prospective PPS
Imperial College Healthcare NHS Trust	AUROC	0.79 (SD 0.01)	0.77	0.68
	FPR	0.21 (SD 0.03)	0.20	0.28

MOTIVATION

**ETHICS** 

**Contributions** Researched interpretable, fair and generalisable models to predict when a patient could switch from IV-to-oral antibiotic treatment, with rigorous and prospective evaluation

> nature communications



Imperial CollegeMOTIVATIONETHICSCO-MORBIDITIESCESSATIONIV TO POCLINICIAN EVALLondonClinician evaluation was conducted through casevignettes, interviews and questionnaires.



**FUTURE WORK** 

CONCLUSION

ealth

amo

antimicrobial

optimisation

Imperial College A greater impact was observed when the AI-IVOS CDSS recommended don't switch.

**CO-MORBIDITIES** 

**ETHICS** 

- 20

15

- 10

MOTIVATION

Heatmap of switch decisions by scenario for patient 7

Intervention

Self efficacy:

15

CDSS

72.32 / 100

3.59/5

3.83 / 5

4.05 / 5

**NO DIFFERENCES** 

11/12 cases

soc

System Usability score:

Perceived usefulness:

Perceived ease of use:

Switch Choice



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**CLINICIAN EVAL** 

**Contributions** Study providing an understanding of the potential use case and benefit of the AI-IVOS CDSS with wider learnings for the AI CDSSs ecosystem

TBC

Imperial CollegeMOTIVATIONETHICSCO-MORBIDITIESCESSATIONIV TO POCLINICIAN EVALFUTURE WORKFuture work includes clinical translation, other partsof prescribing and alternative Al methodologies.



centre for antimicrobial optimisation

CONCLUSION

	2021 2022		2023			23			2024							
Research Questions and Objectives		Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Data access and engineering																
Obtain access to iCARE / ICHT																
Obtain access to MIMIV-IV						ECCMID	]	NEURIPS		ECCMID			AAAI	ECCMID		ICID
Explore and format data for use in ML algorithms																
What performance can AI, EHR based, CDSS for infection management achieve?																
Create initial predictive models																
Enhance models performance and design							$\mathbf{A}$	Antibiotic ces	sation mo	odels						
Investigate optimisation of other aspects of infection management																
Validate models performance on different datasets														to oral switc	n models	
How can multi-morbidity be most appropriately modeled for use in Al CDSS?																
Create an appropriate representation of multi-morbidity													$\land$	Co-morbidit	y in Al	
Explore the relationship between co-morbidities and infection												dihi				
Incorporate co-morbidities into models and assess performance												Items				
What is the most appropriate way to address bias in EHR and AI CDSS?												GSKI				
Investigate bias in existing datasets and algorithms								hought piece bias in AI a	on addre	ssing						
Adapt models to be un-biased, and test performance against initial models																
How can sustained integration and adoption of fair AI CDSS within healthcare systems be achieved?																
Shadow healthcare professionals																
Develop primary research materials																
Conduct patient, public and stakeholder engagement																
Explore implementation barriers and consolidate actionable insights																
Real-world validation and clinical deployment														CDS	S clinician	evaluation
Test CDSS in a real-world clinical setting	$\bigcirc$	CON	IFERENC	E											$\wedge$	
Explore implementation and commercialisation options		סווס		NI.												
Thesis		PUB		N												
Writing		COM	<b>IPLETED</b>	WORKS	STREAM											



London GSK internship exploring the intricacies of ensuring safety and understanding hallucinations in large language models.

Published at ICLR 2024 Workshop on Reliable and Responsible Foundation Models

#### RAMBLA: A FRAMEWORK FOR EVALUATING THE RELIABILITY OF LLMS AS ASSISTANTS IN THE **BIOMEDICAL DOMAIN**

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MOTIVATION

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Imperial College

Gabriela van Bergen Gonzalez Bueno\* GSK.ai gabriela.v.vanbergengonzalez-bueno@gsk.com

Lea Goetz GSK.ai lea.x.goetz@gsk.com

#### ABSTRACT

Large Language Models (LLMs) increasingly support applications in a wide range of domains, some with potential high societal impact such as biomedicine, vet their reliability in realistic use cases is under-researched. In this work we introduce the Reliability AssesMent for Biomedical LLM Assistants (RAmBLA<sup>1</sup>) framework and evaluate whether four state-of-the-art foundation LLMs can serve as reliable assistants in the biomedical domain. We identify prompt robustness, high recall, and a lack of hallucinations as necessary criteria for this use case. We design shortform tasks and tasks requiring LLM freeform responses mimicking real-world user interactions. We evaluate LLM performance using semantic similarity with a ground truth response, through an evaluator LLM.



IV TO PO





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IV TO PO

CONCLUSION



# Imperial College London Artificial Intelligence-Driven Clinical Decision Support for Antibiotic Optimisation.

**CO-MORBIDITIES** 

MOTIVATION

## Conclusion

- Created novel data pipelines and artificial intelligence methodologies •
- Research covers a wide area spanning from fundamental data analysis and • model development, to deploying artificial intelligence-based decision support applications with clinicians
- Tackled key aspects of antibiotic prescribing under-represented in the • literature but impactful regarding a clinical team, their patient, and antimicrobial resistance
- Antimicrobial prescribing and stewardship decisions are are technically, • ethically, and behaviourally complex and numerous barriers exist to implementing AI technology
- Artificial intelligence has potential to tackle antimicrobial resistance • through optimised and individualised antibiotic prescribing decisions

# Imperial College London Thanks everyone for the support.







# Thank you!

William Bolton

Viva

10<sup>th</sup> February 2025



# Appendix

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Prospective evaluation and education are essential for technological adoption, implementation and impact.





We have conducted end user assessment and prospective testing with clinicians in simulated settings

## PRIMARY RESEARCH AND EDUCATION







centre for antimicrobial optimisation

Data often poses a challenge for AI systems in healthcare, particularly those focusing on AMR.

# DATA QUALITY AND MISSINGNESS

- Lack of reliable data on important factors such as absorption
- Appling some important parameters such as co-morbidities to AI systems is combinatorially complex

# HUMAN BEHAVIOUR IS HETEROGENEOUS

 Antimicrobial stewardship is driven by human actions which can be difficult to model and predict





# Antimicrobial stewardship aims to optimise antibiotic decision making.



# STAGES OF ANTIBIOTIC DECISION MAKING



### Antimicrobial stewardship

A coordinated effort and set of practices aimed at **optimising antimicrobial use** and **prolonging their therapeutic life**, to improve infection patient **outcomes** while minimizing the development of **antimicrobial resistance** 

# Artificial intelligence can support optimised antibiotic decision making.



# STAGES OF ANTIBIOTIC DECISION MAKING



Imperial College London Can we create a roadmap for responsibly designing, evaluating and integrating AI in healthcare



### nature medicine

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nature > nature medicine > perspectives > article

Perspective | Published: 19 August 2019

#### Do no harm: a roadmap for responsible machine learning for health care

Jenna Wiens 🖾, Suchi Saria, Mark Sendak, Marzyeh Ghassemi, Vincent X. Liu, Finale Doshi-Velez, Kenneth Jung, Katherine Heller, David Kale, Mohammed Saeed, Pilar N. Ossorio, Sonoo Thadaney-Israni & Anna Goldenberg ☑

Nature Medicine 25, 1337–1340 (2019) Cite this article

33k Accesses | 409 Citations | 704 Altmetric | Metrics

- Choosing the right problems clinical relevance? appropriate data? 2 collaborators? around truth? definition of success? 3 **Rigorous evaluation** and thoughtful ethicist engagement? 45 reporting bias correction? model use? sensical predictions? 6 shared model/code? failure modes? clinical trial? Making it to market medical device? model updates?
  - Developing a useful solution data provenance?

Considering the ethical implications

Deploying responsibly

- prospective performance?
- safety monitoring?

# Many guidelines exist for reporting AI in medicine





#### Box 2: Noteworthy changes and additions to TRIPOD 2015

- New checklist of reporting recommendations to cover prediction model studies using any regression or machine learning method (eg, random forests, deep learning), and harmonise nomenclature between regression and machine learning communities
- New TRIPOD+AI checklist supersedes the TRIPOD 2015 checklist, which should no longer be used
- Particular emphasis on fairness (box 1) to raise awareness and ensure that reports mention whether specific methods were used to deal with fairness. Aspects of fairness are embedded throughout the checklist
- Inclusion of TRIPOD+AI for Abstracts for guidance on reporting abstracts
- Modification of the model performance item recommending that authors evaluate model performance in key subgroups (eg, sociodemographic)
- Inclusion of a new item on patient and public involvement to raise awareness and prompt authors to provide details on any patient and public involvement during the design, conduct, reporting (and interpretation), and dissemination of the study
- Inclusion of an open science section with subitems on study protocols, registration, data sharing and code sharing

TRIPOD=Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis; AI=artificial intelligence.

#### Medicines & Healthcare products Regulatory Agency

#### Guidance

Good Machine Learning Practice for Medical Device Development: Guiding Principles

ealth

optimisation

Kolbinger, F.R., Veldhuizen, G.P., Zhu, J. et al. Reporting guidelines in medical artificial intelligence: a systematic review and meta-analysis. Commun Med **4**, 71 (2024). <u>https://doi.org/10.1038/s43856-024-00492-0</u> Vasey B, Nagendran M, Campbell B, Clifton D A, Collins G S, Denaxas S et al. Reporting guideline for the early stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI BMJ 2022; 377 :e070904 doi:10.1136/bmj-2022-070904 Collins G S, Moons K G M, Dhiman P, Riley R D, Beam A L, Van Calster B et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods BMJ 2024; 385 :e078378 doi:10.1136/bmj-2023-078378

# Imperial College

# Few clinical trials of AI in real clinical practice exist - especially in infectious diseases.





# nature medicine

Explore content V About the journal V Publish with us V

nature > nature medicine > articles > article

#### Article | Published: 21 July 2022

## Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis

Roy Adams, Katharine E. Henry, Anirudh Sridharan, Hossein Soleimani, Andong Zhan, Nishi Rawat, Lauren Johnson, David N. Hager, Sara E. Cosgrove, Andrew Markowski, Eili Y. Klein, Edward S. Chen, Mustapha O. Saheed, Maureen Henley, Sheila Miranda, Katrina Houston, Robert C. Linton, Anushree R. Ahluwalia, Albert W. Wu 🖾 & Suchi Saria

Nature Medicine 28, 1455–1460 (2022) Cite this article

32k Accesses | 73 Citations | 496 Altmetric | Metrics

Han R, Acosta JN, Shakeri Z, Ioannidis JP, Topol EJ, Rajpurkar P. Randomised controlled trials evaluating artificial intelligence in clinical practice: a scoping review. The Lancet Digital Health. 2024 May 1;6(5):e367-73. Adams, R., Henry, K.E., Sridharan, A. et al. Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis. Nat Med 28, 1455–1460 (2022). https://doi.org/10.1038/s41591-022-01894-0

### Imperial College London Al clinical decision support systems are regulated at a minimum as Class II software as a medical device in the UK.



#### **The Journey**

#### Pre-Market

#### Intended Use

The critical first step in the development of AI and health tech products. A clear intended use prioritises safety, effectiveness and gives clarity on how to position your SaMD for success.

READ MORE -

#### **Risk Classification**

The risk level of a medical device or AI product determines the required clinical evidence and regulatory oversight. Read on to learn more!

READ MORE -

2

#### Notified / Approved Body Engagement

To launch a product in the UK or EU, an independent notified body or approved body must review and comply with European legislation, granting UKCA marks.

READ MORE -+

#### **Quality Management** Systems (ISO 13485)

Elevate compliance in medical device manufacturing with our OMS. We cover design, supply, risk management, and CAPAs for a solid regulatory strategy. Read more!

READ MORE -

#### Medical Device File Design

Your MDF provides evidence to demonstrate compliance of the device to all the applicable regulations. Its structure and design is key.

READ MORE -

5

#### MDSAP

The Medical Device Single Audit Programme (MDSAP) streamlines quality management systems by enabling compliance proof through a single audit for five markets.

READ MORE -

#### **Clinical Evaluation Plan**

- The Clinical Evaluation Plan (CEP) is a vital tool in product development, guiding device clinical evaluation through the Valid Clinical Association. Read

more! READ MORE -

#### QMS Deployment & Training

Hardian is an Al-based SaMD company that offers training and guidance to help clients meet international standards for quality management system implementation.

READ MORE -

8

9

10

11

#### Software Verification & Validation

The process of the software development lifecycle is essential to ensure all requirements are met before testing the product in the real world. Read more!

READ MORE -

#### **Clinical Evaluation Report**

The Clinical Evaluation Report (CER) is a crucial document in clinical evaluation, containing development activities and clinical evidence for device marketing.

READ MORE -

#### **Responsible Person (PRRC** and UKRP)

Depending on your jurisdiction of deployment, you may need to appoint responsible persons across these jurisdictions.

READ MORE -

#### Product Registration

Now the hard work is done, registering your product on the relevant regulatory databases is the final step to legally place your product on the market.

READ MORE -

12

**1** Medicines & Healthcare products Regulatory Agency

Guidance

## Software and artificial intelligence (AI) as a medical device

Updated 13 June 2024

https://www.england.nhs.uk/long-read/artificial-intelligence-ai-and-machine-learning/ https://www.hardianhealth.com/regulatory

https://www.gov.uk/government/publications/software-and-artificial-intelligence-ai-as-a-medical-device/software-and-artificial-device/software-and-artificial-device/software-and-artifici

# Usability is also essential for trust and adoption





Journal of Systems and Software Volume 208, February 2024, 111881



Potential effectiveness and efficiency issues in usability evaluation within digital health: A systematic literature review 🖈

Bilal Maqbool 🝳 🖾 , Sebastian Herold 🖾



https://www.mgma.com/mgma-stat/ehr-usability-patient-communications-billing-outrank-ai-as-top-tech-priorities

Maqbool, B. and Herold, S., 2023. Potential effectiveness and efficiency issues in usability evaluation within digital health: A systematic literature review. Journal of Systems and Software, p.111881.

# Are hospitals ready for AI?





# What is ethical and responsible AI?





# Imperial College

# Ensuring models are responsible and ethical becomes more complex as AI advances.



# BIASES

#### **ar** (iv > cs > arXiv:2308.14921

Search... Help | Advand

Computer Science > Computation and Language

[Submitted on 28 Aug 2023]

Gender bias and stereotypes in Large Language Models

#### Hadas Kotek, Rikker Dockum, David Q. Sun

Large Language Models (LLMs) have made substantial progress in the past several months, shattering state-of-the-art benchmarks in many domains. This paper investigates LLMs' behavior with respect to gender stereotypes, a known issue for prior models. We use a simple paradigm to test the presence of gender bias, building on but differing from WinoBias, a commonly used gender bias dataset, which is likely to be included in the training data of current LLMs. We test four recently published LLMs and demonstrate that they express biased assumptions about men and women's occupations. Our contributions in this paper are as follows: (a) LLMs are 3-6 times more likely to choose an occupation that stereotypically aligns with a person's gender; (b) these choices align with people's perceptions better than with the ground truth as reflected in official job statistics; (c) LLMs in fact amplify the bias beyond what is reflected in perceptions or the ground truth; (d) LLMs ignore crucial ambiguities in sentence structure 95% of the time in our study items, but when explicitly promyted, they recognize the ambiguity; (e) LLMs provide explanations for their choices that are factually inaccurate and likely obscure the true reason behind their predictions. That is, they provide explanations of their biased behavior. This highlights a key property of these models: LLMs are trained on imbalanced datasets; as such, even with the recent successes of reinforcement learning with human feedback, they tend to reflect those imbalances back at us. As with other types of societal biases, we suggest that LLMs must be carefully tested to ensure that they treat minoritized individuals and communities equitably.

## HALLUCINATIONS

#### arxiv > cs > arXiv:2311.05232

Help | Advance

#### Computer Science > Computation and Language

[Submitted on 9 Nov 2023]

#### A Survey on Hallucination in Large Language Models: Principles, Taxonomy, Challenges, and Open Questions

#### Lei Huang, Weijiang Yu, Weitao Ma, Weihong Zhong, Zhangyin Feng, Haotian Wang, Qianglong Chen, Weihua Peng, Xiaocheng Feng, Bing Qin, Ting Liu

The emergence of large language models (LLMs) has marked a significant breakthrough in natural language processing (NLP), leading to remarkable advancements in text understanding and generation. Nevertheless, alongside these strides, LLMs exhibit a critical lendency to produce hallucinations, resulting in content that is inconsistent with real-world facts or user inputs. This phenomenon poses substantial challenges to their practical deployment and raises concerns over the reliability of LLMs in real-world scenarios, which attracts increasing attention to detect and mitigate these hallucinations. In this survey, we aim to provide a thorough and in-depth overview of recent advances in the field of LLM hallucinations. We begin with an innovative taxonomy of LLM hallucinations, then delve into the factors contributing to hallucinations. Subsequently, we present a comprehensive overview of hallucination detection methods and benchmarks. Additionally, representative approaches designed to mitigate hallucinations are introduced accordingly. Finally, we analyze the challenges that highlight the current limitations and formulate open questions, aiming to delineate pathways for future research on hallucination in LLMs.

## **PRIVACY LEAKAGE**



#### BLOG POST

ChatGPT and large language models: what's the risk?



# Regulation, frameworks, and standard operating procedures can help ensure responsible AI development.



#### European Parliament

### EU AI Act: first regulation on artificial intelligence

Created: 08-06-2023 - 11:40

The use of artificial intelligence in the EU will be regulated by the AI Act, the world's first comprehensive AI law. Find out how it will protect you.





#### Good Machine Learning Practice for Medical Device Development: Guiding Principles October 2021

The U.S. Food and Drug Administration (FDA), Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP). These guiding principles will help promote safe, effective, and high-quality medical devices that use artificial intelligence and machine learning (AI/ML).

Artificial intelligence and machine learning technologies have the potential to transform health care by deriving new and important insights from the vast amount of data generated during the delivery of health care every day. They use software algorithms to learn from real-world use and in some situations may use this information to improve the product's performance. But they also present unique considerations due to their complexity and the iterative and data-driven nature of their development.

These 10 guiding principles are intended to lay the foundation for developing Good Machine Learning Practice that addresses the unique nature of these products. They will also help cultivate future growth in this rapidly progressing field.

The 10 guiding principles identify areas where the

	Good Machine Learning Practice for Medical Device Development:						
	Guiding Principles						
Mu The	ulti-Disciplinary Expertise Is Leveraged roughout the Total Product Life Cycle	Good Software Engineering and Security Practices Are Implemented					
Clin Rej Po	nical Study Participants and Data Sets Are presentative of the Intended Patient pulation	Training Data Sets Are Independent of Test Sets					
Sel Up	lected Reference Datasets Are Based on Best Available Methods	Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device					
For	cus is Placed on the Performance of the man-Al Team	Testing Demonstrates Device Performance During Clinically Relevant Conditions					
Use	ers Are Provided Clear, Essential ormation	Deployed Models Are Monitored for Performance and Re-training Risks are Managed					

# Define problem and assess risk

Understand data readiness and model design

#### Develop and evaluate

A balance between regulation and guidance is needed for AI





# Comorbidity representation

William Bolton

Viva

10<sup>th</sup> February 2025

# Diagnosis information can be hard to apply to AI systems.







Diseases ordered by count...



Co-morbidities or chronic long-term medical conditions are a **major challenge in healthcare** 

Challenges such as combinatorial complexity, heterogeneity, and a lack of data make using disease data in Al systems difficult Existing AI research on co-morbid patients does not tackle these problems and therefore lacks appropriate representation

### Aim

Creating meaningful embeddings from external medically grounded knowledge, to help overcome such challenges and support downstream AI applications

Dur pipeline leverages a publicly available expert curated healthcare knowledge graph.



mo

Optimized for the mean SNOMED distance between each disease and their nearest neighbor

# We tested our methodologies against two clinically relevant AI tasks.





# Two novel metrics were created for the Similar patient retrieval task.



## SNOMED similarity score

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SNOMED  $sim_{p1,p2} = f(S_{p1,p2}) + f(S_{p2,p1})$ 

where  $S_{p1,p2}$  is a SNOMED distance matrix for the patients co-morbidities

We match each disease of p1 to a disease of p2 so that the matching minimized the following equation:

$$f(A) = \sum_{i=1}^{n} \min_{j \in \{1,...,m\}} \left( 1 - \frac{1}{A_{ij} + 1} \right)$$

where A	$\in$	$\mathbb{R}^{n \times m}$
---------	-------	---------------------------

More similar patients return **smaller** values

# **Charlson Jaccard index**

The Charlson co-morbidity index is a widely adopted clinical tool that classifies some specific co-morbidities to 17 different categories

Charlson Jaccard index<sub>p1,p2</sub> =  $\frac{|C_{p1} \cap C_{p2}|}{|C_{p1} \cup C_{p2}|}$ 

where Crepresents the set of Charlson comorbidities for a particular patient

### More similar patients return larger values



Our pipeline generated meaningful SNOMED disease embeddings.



- Viral and bacterial infectious diseases
- Heart diseases and hypertensive disorders

# SNOMED disease embeddings are informative features for models undertaking clinically relevant predictions.



Table 1: Mean unseen test set AUROC results for supervised learning classification tasks in different populations.

		Year M	lortality	Longleng	th of stay
Features	Model	Overall	Rarest co- morbidities	Overall	Rarest co- morbidities
Charlson co-moribdity categories	Logistic regression	0.65 (SD 0.01)	0.50 (SD <0.01)	0.60 (SD 0.01)	0.50 (SD 0.03)
One hot encodings	Logistic regression	0.79 (SD 0.02)	0.80 (SD 0.23)	0.72 (SD 0.01)	0.55 (SD 0.11)
Random SNOMED disease embeddings	Set transformer	0.80 (SD 0.03)	0.56 (SD 0.33)	0.74(SD 0.02)	0.52 (SD 0.23)
SNOMED disease embeddings	Set transformer	0.82 (SD 0.02)	0.85 (SD 0.14)	0.75 (SD 0.01)	0.61 (SD 0.20)

# Imperial College London Co-morbid patient embeddings finds more similar patients and is consistent across different degrees of rarity and multi-morbidity.

Similarity score distribution 350 Α SNOMED embeddings B One hot encodings 300 250 Table 2: Mean results for the similar patient retrieval 200 Contr 150

task.

Method	SNOMED similarity score	Charlson Jaccard index
One hot encodings	4.40 (SD 2.32)	0.88 (SD 0.30)
Rocheteau's method	3.52 (SD 3.26)	0.69 (SD 0.20)
Co-morbid patient embeddings	1.78 (SD 1.90)	0.84 (SD 0.34)



SNOMED embeddings

Rocheteau score



# Imperial College London Patients identified by our method were selected as the most similar in 60% of questions with a mean winning margin of 40%.





#### Co-morbidities

nerve

entrapment

arthritis

encodings



# Cessation CDSS

William Bolton

Viva

10<sup>th</sup> February 2025

# Antibiotic cessation decision making is complex and under-researched.







One key challenge when treating a patient who has a bacterial infection is determining when it is appropriate to stop antibiotic treatment Numerous studies have shown that on a population level, shorter treatment durations are often non-inferior to longer ones There is a poor understanding of the factors that facilitate or inhibit an individual from receiving a short duration of therapy

### Aim

Utilise a machine learning and synthetic control-based approach to estimate patients total white blood cell count for any given day, if they were to stop vs. continue antibiotic treatment

# Machine learning and synthetic outcome estimation for individualised antimicrobial cessation.





# AUTOENCODER TRAINING



# SYNTHETIC OUTCOME ESTIMATION



Machine learning and synthetic outcome estimation for individualised antimicrobial cessation.



# AUTOENCODER PREDICTIONS

	Metric	Result
	AUROC	0.77 (95% CI 0.73–0.80)
	Accuracy	0.73 (95% CI 0.71–0.75)
Mortality	Precision	0.44 (95% CI 0.36–0.46)
Classification	Recall	0.67 (95% CI 0.61–0.72)
	F1 Score	0.75 (95% CI 0.72–0.78)
	AUPRC	0.55 (95% CI 0.42–0.56)
LOS Regression	RMSE	3.88 (95% CI 3.84–3.92)

# SYNTHETIC OUTCOME ESTIMATION



SCENARIO	DAY(S)		LC	DS	Mortality			
		Mean delta (days, p- value)	MAPE	MAE	RMSE	Mean delta	MAE	AUROC
GTOD	IMPACT	2.71*, <0.01	0.36	3.30	4.80	0.06	0.25	0.66
310P	CONTROL	0.24, 0.60	0.26	1.32	1.93	0.05	0.15	0.72
CONTINUE	IMPACT	-2.09*, <0.01	0.77	2.85	3.16	0.05	0.18	0.67
	CONTROL	0.42*, 0.01	0.48	2.72	3.76	0.07	0.24	0.64



Imperial College London Routinely collected electronic health record data and an autoencoder were used for white blood cell count prediction. DATASET MODEL MIMIC-IV >40,000 ICU patients Autoencoder ICU intravenous antibiotic treatment (days<8) s OUR DATASET 7,867 unique ICU stays ENCODER DECODER → LSTM RNN LSTM RNN Embedding <T> ..... <2> Total white blood 77 The encoder is trained using both cell count (WBC) a supervised loss (L<sub>s</sub>) and features reconstruction loss (L<sub>r</sub>)

The autoencoder achieves reasonable WBC prediction performance and can be used for synthetic scenario estimation.

# AUTOENCODER PREDICTIONS



SYNTHETIC

Our model can estimate patients white blood cell count under alternative antibiotic treatment.



# SYNTHETIC WBC ESTIMATION RESULTS

	1	1			
			WB	C	
Scenario	Day(s)	Mean delta (days, p-value)	MAPE	MAE	RMSE
Stop	Impact	0.71*, <0.01	0.34	2.99	3.89
Stop	Control	0.00, 0.06	0.32	2.50	3.24
Continuo	Impact	-0.31*, <0.01	0.33	2.53	3.18
Continue	Control	0.02*, 0.01	0.32	2.70	3.44

**Evaluation table** 

Embedding visualisation wbc - 20 a fi 15 0 8 pal -2 12 10 Incipal component 1 5 10 -6 15

Machine learning and synthetic outcome estimation for individualised antimicrobial cessation.



# CONSISTENT ESTIMATION RESULTS





# SYNTHETIC OUTCOME ESTIMATION



SCENARIO	DAY(S)		LC	DS	Mortality			
		Mean delta (days, p- value)	MAPE	MAE	RMSE	Mean delta	MAE	AUROC
	IMPACT	2.71*, <0.01	0.36	3.30	4.80	0.06	0.25	0.66
310P	CONTROL	0.24, 0.60	0.26	1.32	1.93	0.05	0.15	0.72
CONTINUE	IMPACT	-2.09*, <0.01	0.77	2.85	3.16	0.05	0.18	0.67
	CONTROL	0.42*, 0.01	0.48	2.72	3.76	0.07	0.24	0.64



# Switch CDSS

William Bolton

Viva

10<sup>th</sup> February 2025

# **Imperial College** Switching from IV-to-oral antibiotic treatment is complex and under-researched.

ELSEVIER





London

One key challenge of stewardship is determining when to switch antibiotics from IV-to-oral administration

Patient A Clinical Infection in Practice me 16 November 2022 10020 Oral step-down for Review March 30, 2020 bacteraemia: An op 3 days **Evaluation of a Paradigm Shift From** stewardship? Intravenous Antibiation to Stephen Platts<sup>a</sup>, Brendan A.I. Payne Ulrich Schwab Therapy for the **1** The American Journal of Medicine me 135, Issue 3, March 2022, Pages 369-379.e1 Endocarditis A Narrative Revie Patient B Oral Is the New IV. Challenging Decades of Brad Spellberg, MD<sup>1</sup>; Henry F. Chambers, Blood and Bone Infection Dogma: A Systematic Review 5 days Noah Wald-Dickler MD <sup>a b c</sup>, Paul D. Holtom MD <sup>a b</sup>, Matthew C. Phillips MD <sup>a</sup> t M. Centor MD <sup>d e</sup>. Rachael, A. Lee MD <sup>d e</sup>. Rachel Baden MD <sup>a</sup>. Brad Spellberg MD <sup>a</sup>

> Numerous studies have shown that oral therapy can be non-inferior to IV

There is a **poor understanding** of the factors that facilitate or inhibit an individual from receiving oral therapy

Aim

Utilise a machine learning and routinely collected clinical parameters to predict whether a patient could be suitable for switching from IV-to-oral antibiotics on any given day

Routinely collected electronic health record data were used, with clinical guided features.





Imperial College

The model achieves generalisable performance across a range of datasets and patient populations.





ANALYSIS



Models predict some patients could be suitable for switching to oral administration earlier



# Fair interpretable machine learning for individualised IV to oral switch decision making.





alth

amo

centre for antimicrobial optimisation



# Traffic light recommendations and informative visual representations improve model interpretability.





#### Day 1

- Highlights
  Both thresholds predict switching is likely not appropriate at this time
- Predictions were correct for 100% of similar examples
- O2 saturation pulseoximetry (feature 4) was of particular interest for these predictions

Feature							Switch to	Switch to oral prediction		
		Importance	1	1 2 3 4 5				oral label	1 <sup>st</sup> threshold	2 <sup>nd</sup> threshold
Patient		-	0.32	0.51	0.37	0.50	0.41	0	0	0
Example	1	0.28	0.38	0.54	0.29	0.48	0.46	0	0	0
	2	0.25	0.31	0.55	0.28	0.51	0.50	0	0	0
	3	0.21	0.29	0.52	0.45	0.52	0.46	0	0	0
	4	0.13	0.32	0.55	0.36	0.51	0.00	0	0	0

#### Day 2

\*

#### Highlights

- Clinical guidance should be sought, model thresholds disagree on whether switching could be appropriate or not at this time
- Predictions were correct for 50% of similar examples (0% for the 1st threshold and 100% for the 2nd threshold)
- O2 saturation pulseoximetry (feature 4) was of particular interest for these predictions

Feature							Switch to	Switch to or	al prediction	
		Importance	1	2 3 4 5		5	oral label	1 <sup>st</sup> threshold	2 <sup>nd</sup> threshold	
Patient	t	-	0.24	0.25	0.28	0.43	0.77	1	1	0
1	1	0.38	0.25	0.20	0.25	0.42	0.73	0	1	0
Example	2	0.12	0.21	0.12	0.20	0.43	0.85	0	1	0

#### \*\* Day 5

#### Highlights

- · Both thresholds predict switching could be appropriate at this time
- Predictions were correct for **75%** of similar examples (75% for the 1<sup>st</sup> threshold and 75% for the 2<sup>nd</sup> threshold)
- Systolic blood pressure (feature 1) and O2 saturation pulseoximetry (feature 4) were of particular interest for these predictions

	Feature							Switch to	Switch to oral prediction	
		Importance	1	1 2 3 4 5					1 <sup>st</sup> threshold	2 <sup>nd</sup> threshold
Patient	t	-	0.16	0.49	0.45	0.37	0.59	1	1	1
Example	1	0.21	0.20	0.58	0.39	0.37	0.45	1	1	1
	2	0.20	0.15	0.47	0.43	0.36	0.70	1	1	1
	3	0.16	0.16	0.43	0.48	0.36	0.76	1	1	1
	4	0.15	0.18	0.49	0.42	0.38	0.59	0	1	1

### Note this system does not cover all aspects of the switch decision making process and should only be used as decision support to highlight when a patient may be suitable for switch assessment





Models demonstrate reasonably fair performance and threshold optimisation can improve results.

Consitius attaileute	Crown	Equalise	d odds demonstrated
Sensitive attribute	Group	Initially	With threshold optimisation
- Cov	Female	$\checkmark$	-
Sex	Male	$\checkmark$	-
	20	$\checkmark$	×
	30	$\checkmark$	$\checkmark$
	40	$\checkmark$	$\checkmark$
٨٥٥	50	$\checkmark$	$\checkmark$
Age	60	$\checkmark$	$\checkmark$
	70	$\checkmark$	$\checkmark$
	80	$\checkmark$	$\checkmark$
	90	×	$\checkmark$
	Asian	$\checkmark$	$\checkmark$
	Black	$\checkmark$	$\checkmark$
	Hispanic	$\checkmark$	$\checkmark$
Race	Native	×	×
	Other	$\checkmark$	$\checkmark$
	Unknown	$\checkmark$	$\checkmark$
	White	$\checkmark$	$\checkmark$
	Medicaid	×	$\checkmark$
Insurance	Medicare	$\checkmark$	$\checkmark$
	Other	$\checkmark$	$\checkmark$

Such technology could provide appropriate decision support and promote switching when appropriate.











Models predict some patients could be **suitable for switching to oral administration earlier** from a clinical parameter, health status perspective

When the difference between the real and predicted switch event was minimal, mean patient LOS outcomes were lower Models only analyse a **snapshot of the patient** and **not all factors** that are clinically used to assess a patient's suitability for switching

# Prospective evaluation was conducted on 40 patients at Imperial NHS Trust against gold-standard pharmacists' recommendations.



Overall absolute temporal difference of 1.23 days (SD 1.42)



Metric	Result
AUROC	0.68
Accuracy	0.70
FPR	0.28

Imperial College

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Temporal difference	Percentage
Early	37.50
Same day	32.50
Late	30

- **Reasonable performance** on small patient sample with a slight preference for **early predictions**
- Such prospective evaluation is essential for highlighting the AI systems **successes and pitfalls**



# Clinician evaluation

William Bolton

Viva

10<sup>th</sup> February 2025

# Forty-two clinicians completed the study with most UK consultant level and specializing in infectious disease.



# **42 PARTICIPANTS**

Demographic	No. (%) of participants
Grade	
Consultant	26~(61.90%)
Other	16~(38.10%)
Medical Speciality	
Infectious Diseases	14~(33.33%)
Microbiology	12~(28.57%)
Pharmacist	6~(14.29%)
Other	10~(23.81%)
Sex	
Male	23~(54.76%)
Female	19~(45.24%)
Age	
20s	4~(9.52%)
30s	17~(40.48%)
40s	12~(28.57%)
50s	6~(14.29%)
60s	2~(4.76%)
Prefer not to say	1~(2.38%)
Age Statistics	
Mean	42
Median	37
Standard Deviation	8.84



London The AI-IVOS CDSS has a greater impact on clinician's decision making when it recommends don't switch.



## NO DIFFERENCES

11/12 cases

Imperial College

### STATISTICALLY SIGNIFICANT DIFFERENCES

### Patient 7 and subgroup analysis for 3 patients





- The system has a greater influence on clinicians when it recommends don't switch
- Participants were **persuaded to take the option** ۲ perceived as safer which matches the culture of cautiousness (40%) and hesitancy to change (24%) reported in interviews.



- Prescribing decisions are **nuanced** and **complex**
- Clinicians could correctly identify incorrect AI recommendations and ignore the support

۲

# Imperial College Decision support explanations had little impact on clinicians' decisions.

London



AI CDSS

Guideline CDSS



- CDSS explanations were not frequently used when available ۲
- Implying that it was the **presence of an AI recommendation** itself driving changes in . decision making
- Explainability methods including displaying **similar** patients (including their outcomes) ۲ and summarizing information in **free text** warrants further research

# The technology was useful, usable and perceived well by participants.





- Clinicians are **reassured** and more confident when given AI recommendations
- The AI CDSS was well perceived being useful, usable and appropriate

# Numerous barriers exist to implementing AI technology with evidence and the system being easy to use essential for adoption.





- There was disagreement on whether healthcare institutions have the necessary **infrastructure to support AI technology**
- **Behavioural factors** such as cautiousness play an important role in antimicrobial prescribing and can act as a **barrier** to technology adoption
- Trust in CDSSs is built through **clinical evidence**, with **ease of use** being essential for adoption



# Case vignette details.

Patient	Intervention Patient		AI CDSS recommendation	Guideline CDSS recommendation	Ground Truth	Data	Group	
1 atient	Arm A	Arm B	AT ODDS recommendation		Ground Truth	Data	Group	
1	CDSS	SOC	Don't switch	Don't switch	Don't switch	ICHT	AI correct	
2	SOC	CDSS	$\mathbf{Switch}$	Switch	Switch	ICHT	AI correct	
3	SOC	CDSS	$\mathbf{Switch}$	Don't switch	Don't switch	ICHT	AI incorrect	
4	CDSS	SOC	Don't switch	Switch	Switch	ICHT	AI incorrect	
5	SOC	CDSS	$\mathbf{Switch}$	Don't switch	-	ICHT	Uncertain	
6	CDSS	SOC	Don't switch	Switch	-	ICHT	Uncertain	
7	CDSS	SOC	Don't switch	Don't switch	Didn't switch	MIMIC	AI correct	
8	SOC	CDSS	$\mathbf{Switch}$	Switch	Switched	MIMIC	AI correct	
9	SOC	CDSS	Potentially switch	Switch	Didn't switch	MIMIC	Uncertain	
10	CDSS	SOC	Don't switch	Switch	Switched	MIMIC	AI incorrect	
11	CDSS	SOC	Switch	Don't switch	Didn't switch	MIMIC	AI incorrect	
12	SOC	CDSS	Potentially switch	Don't switch	Switched	MIMIC	Uncertain	

Table 1: Details of the experimental setup and case vignettes.



Shannon entropy results from the case vignette experiment.

Patient	Shannon entropy
1	0.00
2	0.28
3	0.78
4	0.28
5	0.28
6	0.45
7	1.00
8	0.97
9	0.53
10	1.00
11	1.00
12	0.94

Table 9: Shannon entropy values for the switch decisions made by participants for each patient. Note due to two options (i.e., switch or dont switch) the minimum and maximum possible Shannon entropy values are 0 and 1 respectively.

# Screenshots of the web app used for the case vignette experiment.

ealth

camo

optimisation

