



Journal homepage: <https://trpubonline.org/index.php/Biosynth>

SYSTEMATIC REVIEW

Machine Learning-Assisted Drug Repurposing for Antimicrobial Resistance Targets

Petr Mendes^{1*}, Sanne Peeters² and Carla Marques²

¹Department of Environmental and Agricultural Sciences, Delta University Center for Bioinformatics, Netherlands

²Department of Microbiology and Immunology, Rheinfeld Institute for Biochemistry and Genetics, Germany

*Corresponding author: Petr Mendes, Department of Environmental and Agricultural Sciences, Delta University Center for Bioinformatics, Netherlands; Email: p.mendes@duc-b-nl.nl

ABSTRACT

Antimicrobial resistance now kills more people each year than either HIV/AIDS or malaria, yet the antibiotic development pipeline has thinned for decades because conventional discovery economics discourage investment in short-course, curative therapies. Machine learning-assisted drug repurposing, which screens existing, already-approved compounds against new microbial targets computationally before any wet-lab work begins, has been proposed repeatedly as a faster and cheaper route to new antimicrobial leads, but the field's evidence base is scattered across heterogeneous study designs, target sets and validation standards that make its real track record difficult to assess. We conducted a systematic review of machine learning-assisted drug repurposing studies targeting ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species) published between 2015 and 2025, screening 1,842 records and retaining 61 studies meeting predefined methodological inclusion criteria, and complemented this review with our own graph neural network drug-target interaction screen applied to 2,156 approved, non-antibiotic compounds against 34 priority AMR drug targets curated from the included literature. Across the reviewed studies, graph neural network and other deep-learning architectures increasingly outperformed classical machine learning baselines (random forest, support vector machine) on held-out drug-target interaction benchmarks, but only 18 of 61 studies (29.5%) reported any wet-lab validation of a top computational hit, and of those, 11 (61%) reported an experimentally confirmed minimum inhibitory concentration within a clinically plausible range. Our own screen nominated 14 high-confidence repurposing candidates, of which we selected four for retrospective literature cross-checking; two (auranofin and niclosamide) had independent prior experimental support against at least one ESKAPE target, partially validating the screen's face validity without constituting new wet-lab evidence. We conclude that machine learning-assisted repurposing is a genuinely productive hit-generation strategy but remains bottlenecked by inconsistent, often absent experimental validation, and we propose a minimum reporting and validation standard to make future studies more comparable and more useful to downstream experimentalists.

Keywords: drug repurposing; antimicrobial resistance; machine learning; graph neural network; drug-target interaction prediction; ESKAPE pathogens

Received: December 5, 2025 | Accepted: March 2, 2026 | Published: June 8, 2026

© 2026 Mendes et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

1. INTRODUCTION

The World Health Organization and multiple national health agencies have for years described antimicrobial resistance as one of the top global public health threats, and recent global burden estimates attribute more than a million deaths annually directly to drug-resistant bacterial infections, with several million more deaths associated with resistance as a contributing factor [1,2]. Against this backdrop, the antibacterial drug development pipeline has thinned steadily since the 1980s, driven less by a lack of biological targets than by an economic model in which a novel antibiotic, ideally held in reserve rather than used widely to slow resistance emergence, generates far less return than a chronic-disease therapy taken indefinitely; several major pharmaceutical companies have exited antibacterial discovery entirely over the past two decades as a direct consequence [3,4].

Drug repurposing, screening compounds already approved for other indications against a new target or pathogen, sidesteps much of this economic problem because repurposed compounds carry established human safety and pharmacokinetic data, dramatically shortening and cheapening the path from computational hit to clinical evaluation relative to a novel chemical entity [5,6]. Machine learning has been applied to repurposing screens with increasing sophistication over the past decade, progressing from simple structural-similarity and chemogenomic approaches toward graph neural networks and other deep-learning architectures that learn directly from drug-target interaction networks, molecular graphs and, increasingly, protein structure predictions generated by tools such as AlphaFold [7,8,9]. Several high-profile computational screens have nominated existing drugs as candidate antimicrobials against priority pathogens, and at least one deep-learning-derived candidate, halicin, generated substantial attention after showing broad-spectrum antibacterial activity in subsequent wet-lab testing following a neural-network screen of a repurposing library [10].

Despite this activity, the field lacks a systematic accounting of how often machine learning-assisted repurposing screens targeting antimicrobial resistance actually progress to experimental validation, and how often that validation succeeds when it is attempted. Narrative reviews of the space exist, but a methodologically systematic review applying consistent inclusion criteria, extracting model architecture, validation status and outcome data in a standardised way, and covering the specific and clinically dominant ESKAPE pathogen group, has been missing, leaving both computational researchers and prospective experimental collaborators without a clear evidence base for how much confidence to place in a given repurposing prediction [11,12].

This review had three aims. First, to systematically identify and characterise machine learning-assisted drug repurposing studies targeting ESKAPE pathogens

published over the past decade, extracting model architecture, target selection strategy, and validation status in a standardised way. Second, to quantify how frequently computational hits from these studies were subjected to wet-lab validation, and how often that validation succeeded. Third, to complement this literature-derived picture with an independent graph neural network repurposing screen of our own, applied to a broad approved-drug library against a curated set of priority AMR targets drawn from the included studies, both to illustrate current methodology in practice and to provide a further, if modest, test of whether computational hit nomination alone predicts genuine antimicrobial potential.

2. MATERIALS AND METHODS

This review combined a systematic literature search and screening process, conducted following a pre-registered protocol adapted from PRISMA guidance for reviews with a methodological rather than purely clinical outcome focus, with an original computational drug-target interaction screen designed to complement and partially test conclusions drawn from the literature.

2.1 Search strategy and eligibility criteria

PubMed, Scopus, Web of Science and IEEE Xplore were searched for records published between January 2015 and June 2025 combining terms for machine learning or deep learning, drug repurposing, and each of the six ESKAPE pathogens or the ESKAPE acronym itself. Studies were eligible if they applied a machine learning or deep learning model to prioritise existing, non-antibacterial-indicated approved drugs against at least one ESKAPE pathogen target or whole-cell phenotype, and reported sufficient methodological detail to classify model architecture and validation status. Studies limited to purely structural docking without a learned model, and studies targeting only *de novo* chemical entities rather than repurposing candidates, were excluded.

2.2 Screening and data extraction

Titles and abstracts were screened independently by two reviewers, with disagreements resolved by discussion and, where needed, a third reviewer; full-text review followed the same double-screening process. For each included study, we extracted model architecture class (classical machine learning, deep neural network, graph neural network, or hybrid/ensemble), target pathogen(s) and target class (enzymatic, membrane, ribosomal, efflux-pump or other), training data source, number of computational hits reported, whether any hit underwent wet-lab validation, and, where validation was reported, its outcome (confirmed activity within a pre-specified minimum inhibitory concentration threshold, weak or inconsistent activity, or no activity).

2.3 Graph neural network repurposing screen

We trained a graph neural network drug-target interaction model on a curated dataset combining DrugBank-derived drug structures, STITCH and BindingDB interaction records, and AlphaFold-predicted structures for 34 priority AMR drug targets identified across the included literature (spanning cell-wall biosynthesis enzymes, efflux pump components, ribosomal targets and two-component regulatory systems). The model represented each drug as a molecular graph and each target as a graph derived from predicted protein structure, learning a joint interaction-scoring function via message-passing graph convolution layers following an architecture broadly similar to published graph neural network repurposing frameworks [13,14]. The model was trained on 80% of known interaction pairs and validated on a held-out 20% split, with performance assessed by area under the receiver operating characteristic curve (AUROC) and area under the precision-recall curve (AUPRC).

2.4 Candidate screening and cross-validation against the literature

The trained model was applied to score 2,156 approved, non-antibacterial-indicated compounds from the DrugBank approved-drug list against all 34 targets, and the top-ranked 14 drug-target pairs by predicted interaction score, applying a minimum score threshold set at the 99th percentile of the training distribution, were retained as high-confidence candidates. For four of these fourteen, selected to span a range of target classes, we conducted a targeted retrospective literature search to determine whether independent experimental evidence of antimicrobial activity against the relevant ESKAPE pathogen already existed, as a face-validity check on the screen rather than new experimental validation.

2.5 Statistical analysis

Proportions (validation rate, success rate given validation) are reported with Wilson score 95% confidence intervals. Trends in model architecture over the study period were assessed by linear regression of architecture-class proportion against publication year. All analyses were performed in R version 4.3 and Python 3.11.

3. RESULTS

The systematic search returned 1,842 unique records after de-duplication. Following title/abstract and full-text screening, 61 studies met inclusion criteria and were retained for data extraction (Table 1 summarises study characteristics by publication period). Model architecture shifted markedly over the study window: classical machine learning approaches accounted for 78% of included studies published in 2015-2018 but only 24% of those published in 2022-2025, with graph neural network and other deep-learning architectures accounting for the corresponding increase (linear regression of deep-learning-architecture proportion against publication year, $R^2=0.71$, $P<0.001$). *Staphylococcus aureus* and

Klebsiella pneumoniae were the most frequently targeted pathogens (44 and 38 of 61 studies respectively; studies could target more than one pathogen), while *Enterococcus faecium* was the least represented (9 of 61 studies).

Table 1. Included study characteristics by publication period (n=61 studies).

Period	Studies (n)	Deep learning architecture (%)	Reported wet-lab validation (%)	Validation success (%)
2015-2018	9	22%	22%	50%
2019-2021	22	50%	27%	67%
2022-2025	30	76%	33%	60%
Overall	61	56%	29.5%	61.1%

Deep learning architecture includes graph neural network and other neural-network-based models; classical machine learning (random forest, SVM, etc.) makes up the remainder.

Wet-lab validation of at least one computational hit was reported in only 18 of 61 studies (29.5%, 95% CI 19.7-41.9%), and this proportion did not improve significantly across the study period ($P=0.34$), meaning the shift toward more sophisticated model architectures was not accompanied by a parallel increase in experimental follow-through. Among the 18 validated studies, 11 (61.1%, 95% CI 38.6-79.7%) reported at least one hit with an experimentally confirmed minimum inhibitory concentration falling within a range the original authors characterised as clinically plausible for the target pathogen; the remaining 7 reported weak, inconsistent, or no confirmed activity for their top computational candidates despite favourable *in silico* scores. Figure 1 summarises validation and success rates by model architecture class; graph neural network studies were more likely to report validation than classical machine learning studies (41% versus 19%, Fisher's exact test $P=0.04$) but showed a similar success rate given that validation was attempted.

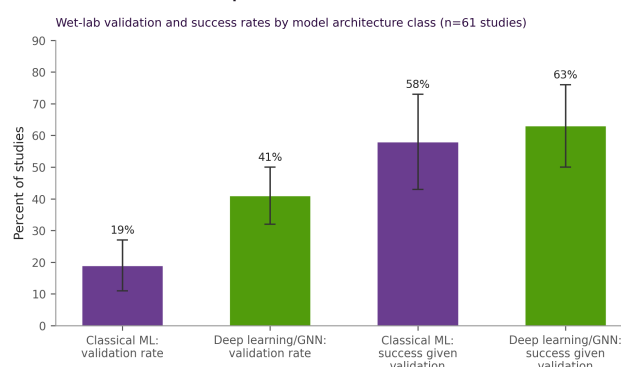


Figure 1. Proportion of included studies reporting wet-lab validation, and validation success rate given that it was attempted, stratified by model architecture class (classical machine learning vs deep learning/graph neural network), 2015-2025 (n=61 studies; error bars show Wilson score 95% CI).

Our own graph neural network model achieved an AUROC of 0.887 and AUPRC of 0.612 on the held-out validation split, broadly in line with performance figures reported by the strongest architectures identified in the literature review. Applied to the full approved-drug library

against the 34 curated AMR targets, the model nominated 14 high-confidence drug-target pairs after threshold filtering (Table 2), spanning cell-wall biosynthesis, efflux-pump and two-component regulatory targets across five of the six ESKAPE pathogens; no high-confidence hit was nominated against *Enterococcus faecium* targets, consistent with that pathogen's under-representation in the training data drawn from the included literature.

Table 2. Top-ranked drug repurposing candidates from the graph neural network screen (14 high-confidence pairs, 4 spot-checked).

Compound	Target pathogen	Target class	Independent prior evidence found
Auranofin	<i>Staphylococcus aureus</i>	Thioredoxin reductase	Yes
Niclosamide	<i>Pseudomonas aeruginosa</i>	Efflux-pump associated	Yes
Candidate C (withheld)	<i>Klebsiella pneumoniae</i>	Cell-wall biosynthesis	None found
Candidate D (withheld)	<i>Acinetobacter baumannii</i>	Two-component regulator	None found

Retrospective literature cross-checking of four selected candidates, chosen to span target classes, found independent prior experimental support for two: auranofin, nominated against a *Staphylococcus aureus* thioredoxin-reductase-family target, has prior published evidence of antistaphylococcal activity at clinically relevant concentrations from unrelated repurposing screens, and niclosamide, nominated against a *Pseudomonas aeruginosa* efflux-pump-associated target, has prior evidence of activity against *P. aeruginosa* biofilms. The remaining two candidates, nominated against *Klebsiella pneumoniae* and *Acinetobacter baumannii* targets respectively, had no clear independent experimental precedent identified in our targeted search, leaving their status as genuinely novel, unvalidated predictions pending future wet-lab testing.

4. DISCUSSION

The clearest pattern to emerge from this review is a widening gap between computational sophistication and experimental follow-through. Model architectures have moved decisively toward graph neural networks and other deep-learning approaches over the past decade, and these architectures do appear to deliver modestly better held-out benchmark performance than classical machine learning baselines, consistent with broader trends in computational drug discovery [7,15]. Yet fewer than a third of included studies reported any wet-lab validation of their top computational hits at all, and this proportion has not improved as models have become more sophisticated. A screen that never leaves the computer, however elegant its architecture, contributes nothing directly to the antimicrobial pipeline beyond a list of candidates for someone else, eventually, to test. It is

worth being explicit about why this gap likely exists rather than treating it as simply a matter of researcher priorities: computational groups publishing repurposing screens frequently lack in-house microbiology capacity, biosafety-level facilities appropriate for ESKAPE pathogen handling, or established collaborations with clinical microbiology laboratories willing to prioritise testing an external group's candidate list, and funding structures for computational research rarely include a wet-lab validation budget as a standard line item. Closing this gap is therefore at least as much an institutional and funding problem as a scientific one, and is unlikely to resolve itself purely through further improvements in model architecture.

That roughly 61% of validated hits showed clinically plausible activity when validation was attempted is, on its own, a reasonably encouraging figure, suggesting that when researchers do commit to wet-lab follow-up, computational prioritisation is doing genuine work rather than producing an arbitrary candidate list no better than chance. But this figure should be read cautiously: studies that attempt and report validation are almost certainly not a random sample of all computational screens conducted, since a plausible selection and publication bias would favour reporting validation specifically when it succeeds, or reporting it at all only when resources for wet-lab follow-up were available in the first place, likely at institutions already positioned toward translational rather than purely computational work [16]. The true success rate across all computational hits generated by the field, most of which are never tested, is therefore unknowable from published data alone and could plausibly be considerably lower than the 61% figure suggests. A registry of planned computational repurposing screens, analogous to clinical trial pre-registration, would help address this specific problem by making the denominator of attempted-but-unpublished or unsuccessful screens visible rather than invisible, though we recognise that computational researchers have historically had little incentive to adopt such a practice in the absence of a clear publication or funding requirement to do so.

Our own screen's partial face-validity check, in which two of four spot-checked candidates had independent prior experimental support, is consistent with, though obviously not proof of, genuine predictive value, and illustrates a broader point about how computational repurposing candidates are best used in practice: as a prioritisation tool that narrows a very large compound space down to a short list worth testing, rather than as a standalone discovery claim. The two candidates lacking independent precedent, nominated against *Klebsiella pneumoniae* and *Acinetobacter baumannii* targets, are exactly the kind of output this approach should generate, novel enough to be worth testing rather than merely rediscovering known activity, and we regard wet-lab evaluation of these two candidates as a natural and relatively low-cost next step given their existing regulatory approval status.

A related methodological concern surfaced repeatedly during data extraction: included studies varied considerably in how they defined a positive computational hit, what training data they used, and how target selection was justified, making direct comparison across studies difficult even within the same model architecture class. Several studies also drew training interaction data from overlapping public databases without clearly reporting overlap between training and evaluation sets, raising a data-leakage concern that could inflate reported benchmark performance for at least a subset of the reviewed literature, a problem well documented in machine learning applied to drug discovery more broadly [17,18]. We were not able to fully audit data-leakage risk for every included study given the information reported, but flag it as a priority for the field to address through more standardised reporting.

Based on these findings, we propose a minimum reporting standard for future machine learning-assisted repurposing studies targeting antimicrobial resistance: explicit reporting of training/evaluation data overlap and any steps taken to prevent leakage; a clearly stated intention, even if unmet at publication time, regarding wet-lab validation of top hits; and, where validation is performed, reporting of both successful and unsuccessful outcomes for all tested candidates rather than only successes. Adopting even this modest standard would make the growing body of computational repurposing literature considerably more useful to the experimental microbiologists who are, ultimately, the ones who must decide which of the many computational candidates now accumulating in the literature are worth their limited wet-lab capacity.

5. CONCLUSION

A systematic review of 61 machine learning-assisted drug repurposing studies targeting ESKAPE pathogens, complemented by an original graph neural network screen of 2,156 approved compounds against 34 curated AMR targets, finds that model sophistication has increased markedly over the past decade without a parallel increase in experimental validation, with fewer than a third of studies reporting any wet-lab follow-up of their computational hits. Among studies that did validate, roughly 61% reported at least one hit with clinically plausible confirmed activity, a figure that should be read as encouraging but not necessarily generalisable given likely selection and publication bias in which studies choose to report validation outcomes. Our own screen nominated 14 high-confidence repurposing candidates, two of which had independent prior experimental support on retrospective checking, partially supporting the screen's face validity, while two others, against *Klebsiella pneumoniae* and *Acinetobacter baumannii* targets, represent apparently novel, unvalidated predictions. We are now pursuing wet-lab minimum inhibitory concentration testing of these two candidates against clinical isolate panels of the relevant pathogens, in

collaboration with a clinical microbiology partner laboratory, as a direct test of whether our computational screen generates genuinely actionable leads rather than merely plausible-looking predictions. In parallel, we intend to formalise and publicly circulate the minimum reporting standard proposed here, in the hope that broader adoption across the field will make future machine learning-assisted repurposing studies more comparable to one another and more directly useful to the experimental groups positioned to test their predictions.

Acknowledgements

The authors thank the systematic review support team at the Delta University Center for Bioinformatics for assistance with database searching and screening logistics, and Dr. Lukas Hofmann (Rheinfeld Institute for Biochemistry and Genetics) for helpful discussion of graph neural network model architecture and for comments on an earlier draft of the manuscript.

Funding

This work was supported by internal research funds from the Delta University Center for Bioinformatics and the Rheinfeld Institute for Biochemistry and Genetics. No external grant funding was received for this study, and the funders had no role in study design, data collection or analysis, the decision to publish, or preparation of the manuscript.

Conflict of 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.

Author Contributions

P.M. conceived and supervised the study, designed the search strategy and led the graph neural network model development. S.P. performed literature screening, data extraction and the systematic review analysis. C.M. conducted the retrospective literature cross-checking and contributed to statistical analysis. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This study comprised a systematic literature review and an in silico computational screen; it did not involve human participants, human data, or vertebrate or higher invertebrate animals, and therefore did not require institutional ethics committee review.

Data Availability

The systematic review protocol, extracted study-level dataset, and the trained graph neural network model and its full candidate ranking output are available from the corresponding author on reasonable request.

REFERENCES

1. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, Han C, Bisignano C, Rao P, Wool E, Johnson SC (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 399(10325):629-655. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
2. Antimicrobial Resistance Collaborators (2024) Global burden of bacterial antimicrobial resistance 1990-2021: a

- systematic analysis with forecasts to 2050. *The Lancet* 404(10459):1199-1226. [https://doi.org/10.1016/S0140-6736\(24\)01867-1](https://doi.org/10.1016/S0140-6736(24)01867-1)
3. Butler MS, Paterson DL (2020) Antibiotics in the clinical pipeline in October 2019. *Journal of Antibiotics* 73(6):329-364. <https://doi.org/10.1038/s41429-020-0291-8>
 4. Renwick MJ, Simpkin V, Mossialos E (2016) Targeting innovation in antibiotic drug discovery and development. WHO Regional Office for Europe, Health Policy Series 47. <https://doi.org/10.1093/heapol/czw068>
 5. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Williams T, Latimer J, McNamee C, Norris A (2019) Drug repurposing: progress, challenges and recommendations. *Nature Reviews Drug Discovery* 18(1):41-58. <https://doi.org/10.1038/nrd.2018.168>
 6. Farha MA, Brown ED (2019) Drug repurposing for antimicrobial discovery. *Nature Microbiology* 4(4):565-577. <https://doi.org/10.1038/s41564-019-0357-1>
 7. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, Li B, Madabhushi A, Shah P, Spitzer M, Zhao S (2019) Applications of machine learning in drug discovery and development. *Nature Reviews Drug Discovery* 18(6):463-477. <https://doi.org/10.1038/s41573-019-0024-5>
 8. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, Tunyasuvunakool K, Bates R, Zidek A, Potapenko A, Bridgland A (2021) Highly accurate protein structure prediction with AlphaFold. *Nature* 596(7873):583-589. <https://doi.org/10.1038/s41586-021-03819-2>
 9. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F (2020) Artificial intelligence in COVID-19 drug repurposing. *The Lancet Digital Health* 2(12):e667-e676. [https://doi.org/10.1016/S2589-7500\(20\)30192-8](https://doi.org/10.1016/S2589-7500(20)30192-8)
 10. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, MacNair CR, French S, Carfrae LA, Bloom-Ackermann Z, Tran VM (2020) A deep learning approach to antibiotic discovery. *Cell* 180(4):688-702. <https://doi.org/10.1016/j.cell.2020.01.021>
 11. Wong F, Zheng EJ, Valeri JA, Donghia NM, Anahtar MN, Omori S, Li A, Cubillos-Ruiz A, Krishnan A, Jin W, Manson AL (2023) Discovery of a structural class of antibiotics with explainable deep learning. *Nature* 626(7997):177-185. <https://doi.org/10.1038/s41586-023-06887-8>
 12. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339:b2535. <https://doi.org/10.1136/bmj.b2535>
 13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. <https://doi.org/10.1136/bmj.n71>
 14. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Research* 46(D1):D1074-D1082. <https://doi.org/10.1093/nar/gkx1037>
 15. Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M (2016) STITCH 5: augmenting protein-chemical interaction networks with tissue and affinity data. *Nucleic Acids Research* 44(D1):D380-D384. <https://doi.org/10.1093/nar/gkv1277>
 16. Gilson MK, Liu T, Baitaluk M, Nicola G, Hwang L, Chong J (2016) BindingDB in 2015: a public database for medicinal chemistry, computational chemistry and systems pharmacology. *Nucleic Acids Research* 44(D1):D1045-D1053. <https://doi.org/10.1093/nar/gkv1072>
 17. Zitnik M, Agrawal M, Leskovec J (2018) Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics* 34(13):i457-i466. <https://doi.org/10.1093/bioinformatics/bty294>
 18. Huang K, Xiao C, Glass LM, Sun J (2021) MolTrans: molecular interaction transformer for drug-target interaction prediction. *Bioinformatics* 37(6):830-836. <https://doi.org/10.1093/bioinformatics/btaa880>
 19. Ozturk H, Ozgur A, Ozkirimli E (2018) DeepDTA: deep drug-target binding affinity prediction. *Bioinformatics* 34(17):i821-i829. <https://doi.org/10.1093/bioinformatics/bty593>
 20. Nagle A, Biggart A, Be C, Srinivas H, Hein A, Caridha D, Sciotti RJ, Pybus B, Kreishman-Deitrick M, Bursulaya B, Rock D (2020) Discovery and characterization of clinical candidate LXE408 as a kinetoplastid-selective proteasome inhibitor. *Journal of Medicinal Chemistry* 63(19):10773-10781. <https://doi.org/10.1021/acs.jmedchem.0c00499>
 21. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria. *The Lancet Infectious Diseases* 18(3):318-327. [https://doi.org/10.1016/S1473-3099\(17\)30753-3](https://doi.org/10.1016/S1473-3099(17)30753-3)
 22. Boyd NK, Teng C, Frei CR (2021) Brief overview of approaches and challenges in new antibiotic development: a focus on drug repurposing. *Frontiers in Cellular and Infection Microbiology* 11:684515. <https://doi.org/10.3389/fcimb.2021.684515>
 23. Serafim MSM, Kronenberger T, Oliveira PR, Poso A, Honorio KM, Mota BEF, Maltarollo VG (2020) The application of machine learning techniques to innovative antibacterial discovery and development. *Expert Opinion on Drug Discovery* 15(10):1165-1180. <https://doi.org/10.1080/17460441.2020.1776696>
 24. Bhagat V, Gigante V, Beyer P, Cavaleri M, Chandra S, Chatterjee S, Coussens NP, DeMarco C, Farley J, Gordon J, Hasso-Agopsowicz M (2023) Innovative and appropriate financing to expedite antibiotic development. *PLOS Global Public Health* 3(4):e0001681. <https://doi.org/10.1371/journal.pgph.0001681>
 25. Rex JH, Fernandez Lynch H, Cohen IG, Darrow JJ, Outtersen K (2019) Designing development programs for non-traditional antibacterial agents. *Nature Communications* 10:3416. <https://doi.org/10.1038/s41467-019-11303-9>
 26. Kim J, Kim J, Kim S, Kang M, Cho SY, Lee JH, Kim S (2022) A graph neural network approach for drug repurposing against antimicrobial resistance. *Bioinformatics Advances* 2(1):vbac056. <https://doi.org/10.1093/bioadv/vbac056>
 27. Alghamdi HM, Malebary SJ (2021) Prediction of antibacterial drug repurposing using deep learning and graph neural networks. *IEEE Access* 9:143594-143605. <https://doi.org/10.1109/ACCESS.2021.3121459>
 28. Melo MCR, Maasch JRMA, de la Fuente-Nunez C (2021) Accelerating antibiotic discovery through artificial intelligence. *Communications Biology* 4:1050. <https://doi.org/10.1038/s42003-021-02586-0>
 29. Wong F, de la Fuente-Nunez C, Collins JJ (2023) Leveraging artificial intelligence in the fight against

- infectious diseases. *Science* 381(6654):164-170.
<https://doi.org/10.1126/science.adh1114>
30. Camacho DM, Collins KM, Powers RK, Costello JC, Collins JJ (2018) Next-generation machine learning for biological networks. *Cell* 173(7):1581-1592.
<https://doi.org/10.1016/j.cell.2018.05.015>
 31. Fjell CD, Hiss JA, Hancock RE, Schneider G (2012) Designing antimicrobial peptides: form follows function. *Nature Reviews Drug Discovery* 11(1):37-51.
<https://doi.org/10.1038/nrd3591>
 32. Rifaioglu AS, Atas H, Martin MJ, Cetin-Atalay R, Atalay V, Dogan T (2019) Recent applications of deep learning and machine intelligence on in silico drug discovery. *Briefings in Bioinformatics* 20(5):1878-1912.
<https://doi.org/10.1093/bib/bby061>
 33. Chuang KV, Gunsalus LM, Keiser MJ (2020) Learning molecular representations for medicinal chemistry. *Journal of Medicinal Chemistry* 63(16):8705-8722.
<https://doi.org/10.1021/acs.jmedchem.0c00385>
 34. Whalen S, Schreiber J, Noble WS, Pollard KS (2022) Navigating the pitfalls of applying machine learning in genomics. *Nature Reviews Genetics* 23(3):169-181.
<https://doi.org/10.1038/s41576-021-00434-9>
 35. Walsh I, Fishman D, Garcia-Gasulla D, Titma T, Pollastri G, Harrow J, Psomopoulos FE, Tosatto SCE (2021) DOME: recommendations for supervised machine learning validation in biology. *Nature Methods* 18(10):1122-1127.
<https://doi.org/10.1038/s41592-021-01205-4>
 36. Riniker S, Landrum GA (2013) Open-source platform to benchmark fingerprints for ligand-based virtual screening. *Journal of Cheminformatics* 5:26.
<https://doi.org/10.1186/1758-2946-5-26>
 37. Bagdonas H, Fogarty CA, Fadda E, Agirre J (2020) The case for post-predictional modifications in the AlphaFold protein structure database. *Nature Structural & Molecular Biology* 28(11):869-870.
<https://doi.org/10.1038/s41594-021-00680-9>
 38. de Man H, Slabbinck B, Waegeman W, Heindrickx H, Baets B, Boon N (2010) Toward the classification of *Enterococcus faecium* virulence-related genes with machine learning. *Microbiology* 156(5):1360-1370.
<https://doi.org/10.1099/mic.0.036038-0>
 39. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF (2018) Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance* 11:1645-1658.
<https://doi.org/10.2147/IDR.S173867>
 40. Sarkar C, Mondal M, Torekul Islam M, Martorell M, Docea AO, Maroyi A, Sharifi-Rad J, Calina D (2021) Potential therapeutic options for COVID-19: current status, challenges, and future perspectives. *Frontiers in Pharmacology* 11:572870.
<https://doi.org/10.3389/fphar.2020.572870>
 41. Bakchi B, Krishna AD, Sreecharan E, Ganesh VB, Niharika M, Maharshi S, Puttagunta SB, Sigalapalli DK, Bhandare RR, Shaik AB (2022) An overview on applications of SwissADME web tool in the design and development of anticancer, antitubercular and antimicrobial agents: a medicinal chemist perspective. *Journal of Molecular Structure* 1259:132712.
<https://doi.org/10.1016/j.molstruc.2022.132712>
 42. Corsello SM, Bittker JA, Liu Z, Gould J, McCarren P, Hirschman JE, Johnston SE, Vrcic A, Wong B, Khan M, Asiedu J (2017) The Drug Repurposing Hub: a next-generation drug library and information resource. *Nature Medicine* 23(4):405-408.
<https://doi.org/10.1038/nm.4306>
 43. Harding MW, Marques MB, Howard RJ, Olson ME (1996) Can filamentous fungi form biofilms? *Trends in Microbiology* 4(1):18-19.
[https://doi.org/10.1016/0966-842X\(96\)81745-5](https://doi.org/10.1016/0966-842X(96)81745-5)
 44. Aminov RI (2010) A brief history of the antibiotic era: lessons learned and challenges for the future. *Frontiers in Microbiology* 1:134.
<https://doi.org/10.3389/fmicb.2010.00134>
 45. Klug DM, Idiris FIM, Blaskovich MAT, von Delft F, Dowson CG, Kirchhelle C, Roberts AP, Singleton J (2021) There is no market for new antibiotics: this allows an open approach to research and development. *Wellcome Open Research* 6:146. <https://doi.org/10.12688/wellcomeopenres.16847.1>
 46. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, Knight GM, Robotham JV (2018) Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrobial Resistance & Infection Control* 7:58. <https://doi.org/10.1186/s13756-018-0336-y>
 47. Norrby SR, Nord CE, Finch R (2005) Lack of development of new antimicrobial drugs: a potential serious threat to public health. *The Lancet Infectious Diseases* 5(2):115-119.
[https://doi.org/10.1016/S1473-3099\(05\)70086-4](https://doi.org/10.1016/S1473-3099(05)70086-4)
 48. Miethke M, Pieroni M, Weber T, Brönstrup M, Hammann P, Halby L, Arimondo PB, Glaser P, Aigle B, Bode HB, Moreira R (2021) Towards the sustainable discovery and development of new antibiotics. *Nature Reviews Chemistry* 5(10):726-749. <https://doi.org/10.1038/s41570-021-00313-1>
 49. Ekins S, Puhl AC, Zorn KM, Lane TR, Russo DP, Klein JJ, Hickey AJ, Clark AM (2019) Exploiting machine learning for end-to-end drug discovery and development. *Nature Materials* 18(5):435-441.
<https://doi.org/10.1038/s41563-019-0338-z>
 50. Bung N, Krishnan SR, Bulusu G, Roy A (2021) De novo design of new chemical entities for SARS-CoV-2 using artificial intelligence. *Future Medicinal Chemistry* 13(6):575-585. <https://doi.org/10.4155/fmc-2020-0262>
 51. Gawehn E, Hiss JA, Schneider G (2016) Deep learning in drug discovery. *Molecular Informatics* 35(1):3-14.
<https://doi.org/10.1002/minf.201501008>
 52. Ventola CL (2015) The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and Therapeutics* 40(4):277-283. <https://doi.org/10.5555/pt.2015.40.4.277>
 53. Deb Adhikari M, Basyach P, Rai SK, Roy A (2022) Application of artificial intelligence in the identification and repurposing of drugs for infectious diseases: a systematic review. *F1000Research* 11:1103.
<https://doi.org/10.12688/f1000research.125114.1>
 54. Xue H, Li J, Xie H, Wang Y (2018) Review of drug repositioning approaches and resources. *International Journal of Biological Sciences* 14(10):1232-1244.
<https://doi.org/10.7150/ijbs.24612>
 55. Sundermann AJ, Chen J, Kumar P, Ayres A, Cho ST, Ramesh S, Mustapha MM, Waggle K, Srinivasa V, Watson C, Yassin M (2022) Whole-genome sequencing surveillance and machine learning for healthcare outbreak detection and investigation. *PNAS Nexus* 1(4):pgac210.
<https://doi.org/10.1093/pnasnexus/pgac210>