

Review Article

Immunoinformatics: Expanding frontiers and emerging tools in bioinformatics for immunology

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ABSTRACT

The interdisciplinary field of immunoinformatics, which combines immunology with computational biology, is revolutionising vaccine development and epitope identification. This paper explores recent advancements, tools and methodologies in immunoinformatics, highlighting their potential applications in creating vaccines for diseases such as COVID-19, influenza, malaria, tuberculosis, dengue and pneumonia. We discuss how tools such as BepiPred 3.0, SVMTrip, IFNepitope, Vaxijen, immune epitope database, NetCTL and PEP-FOLD can enhance the precision and efficiency of vaccine design. In addition, we address the challenges and future directions in the field, emphasising the need for improved computational models, better data integration and rigorous experimental validation to bridge the gap between *in silico* predictions and real-world applications.

Keywords: Computational tools, Disease-specific vaccines, Epitope identification, Immunoinformatics, Vaccine development

INTRODUCTION

Specific regions of an antigen molecule that are recognised and bound by a B- or a T-cell receptor (TCR) are referred to as epitopes. Epitopes, also known as antigenic determinants, are specific parts of a virus or bacteria that the immune system can 'see' and respond to. You can think of them like barcodes on a product – each one is unique, and once scanned, the immune system knows how to respond. Identifying these barcodes helps researchers design vaccines that train the immune system to recognise and attack the pathogen before it causes illness. Researchers can identify possible targets for immune responses by predicting and modelling epitopes with the aid of databases and computational techniques. The efficacy and safety of epitope-based vaccinations and immunotherapies can be enhanced by customising their design to trigger certain immune reactions, thanks to this predictive capability. Furthermore, monitoring immune escape mechanisms and developing broad-spectrum vaccinations are aided by knowledge of epitope variability and conservation amongst various diseases and strains. Therefore, epitopes are essential for developing personalised medicine and improving our capacity to use novel immunological techniques to fight infectious diseases. Immunoinformatics has become a powerful tool in the field of immunology, renovating the way we approach epitope discovery and vaccine development.^[1] Using a medley of genomics, proteomics and machine learning, immunoinformatics hastens the development of vaccines against infectious diseases, highlighting newly developing pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^[2] This fusion of

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immunological principles with computational approaches not only accelerates research but also presents a capable avenue for countering risks to global health.^[3]

The application of complex tools and algorithms for epitope prediction and vaccine formulation is a fundamental component of immunoinformatics.^[4] Amongst these, VaxiJen, immune epitope database (IEDB), NetCTL, PEP-FOLD, BepiPred 2.0, SVMTrip and IFNepitope are noteworthy instruments that are essential for determining immunogenic peptides, mapping epitopes and streamlining the peptide vaccine design process.^[5] Immunoinformatics enhances the development of successful vaccines and therapies by streamlining the processes of antigen selection, toxicity prediction, allergenicity evaluation and major histocompatibility complex (MHC)-I and II binding epitope prediction by utilising computer techniques.^[6] Immunoinformatics, therefore, is not limited to a single pathogen; rather, it tackles a range of infectious disorders, such as COVID-19, human papillomavirus and other newly discovered agents.^[7] Researchers can react quickly to changing health risks thanks to this adaptability, especially when it comes to immune-evading and multidrug-resistant bacteria.^[8]

A proactive and effective response to worldwide pandemics is made possible by the incorporation of immunoinformatics into vaccine research, which guarantees that prospective candidates go through a thorough efficacy and safety review before clinical trials.^[9]

Essentially, a new era in vaccine design and epitope identification is brought about by the integration of immunology and computer approaches in the discipline of immunoinformatics. Immunoinformatics helps fight infectious diseases and has the potential to improve immunological protection globally by providing quick and affordable solutions. This study delves into the latest developments, trends and uses of immunoinformatics tools to transform immunology and tackle urgent health issues.

APPLICATIONS AND CASE STUDIES

Before citing the specific case studies, a brief overview of a few diseases immunoinformatics research has yielded significant results is being shared in order to highlight the versatility of this protocol against diseases caused by extremely different pathogens. A summary of key immunoinformatics applications across infectious diseases is presented in Table 1.

INFLUENZA VIRUS

Pathogen

The influenza virus, which belongs to the *Orthomyxoviridae* family, is the causative agent of influenza or flu. There are

four types of influenza viruses: A, B, C and D, with types A and B causing seasonal epidemics.^[10]

Carriers and transmission

Influenza viruses are primarily spread through respiratory droplets when an infected person coughs, sneezes or talks. It can also spread by touching surfaces contaminated with the virus and then touching the face. Humans are the primary hosts, but influenza-A viruses can also infect birds and mammals.

Symptoms and effects

Symptoms include fever, chills, muscle aches, cough, congestion, runny nose, headaches and fatigue. Severe cases can lead to pneumonia, respiratory failure and death, especially in high-risk groups such as the elderly, young children and those with weakened immune systems.^[11]

MALARIA

Pathogen

Malaria is caused by *Plasmodium* parasites, with *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*. *Plasmodium malariae* and *Plasmodium knowlesi* are the species that infect humans.^[12]

Carriers and transmission

The disease is transmitted through the bite of infected female *Anopheles* mosquitoes. The parasite undergoes part of its lifecycle in the mosquito and part in the human host.

Symptoms and effects

Symptoms include fever, chills, headache, nausea, vomiting, muscle pain and fatigue. Severe malaria can cause anaemia, respiratory distress and cerebral malaria, which can be fatal if not treated promptly.^[13]

TUBERCULOSIS (TB)

Pathogen

TB is caused by the bacterium *Mycobacterium tuberculosis*.^[14]

Carriers and transmission

TB is an airborne disease that spreads when a person with active TB disease of the lungs or throat coughs, speaks or sings, releasing tiny droplets containing the bacteria into the air. Close contacts are most at risk.

Symptoms and effects

Common symptoms include a persistent cough, chest pain, coughing up blood or sputum, weakness, weight loss, fever and night sweats. If left untreated, TB can be fatal, primarily affecting the lungs, but it can also affect other parts of the body.^[15]

DENGUE FEVER

Pathogen

Dengue fever is caused by the dengue virus (DENV), which is a member of the *Flaviviridae* family. There are four serotypes of the virus: DENV-1, DENV-2, DENV-3 and DENV-4.^[16]

Carriers and transmission

The virus is transmitted to humans through the bite of infected *Aedes* mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*.

Symptoms and effects

Symptoms include high fever, severe headache, pain behind the eyes, joint and muscle pain, rash and mild bleeding. Severe dengue, also known as dengue haemorrhagic fever or dengue shock syndrome, can cause severe bleeding, organ failure and death.^[17]

COVID-19

Pathogen

COVID-19 is caused by the SARS-CoV-2 virus, a novel coronavirus first identified in December 2019.^[18]

Carriers and transmission

The virus spreads primarily through respiratory droplets from coughs, sneezes or talking. It can also be transmitted by touching surfaces contaminated with the virus and then touching the face.

Symptoms and effects

Symptoms range from mild to severe and include fever, cough, shortness of breath, fatigue, muscle or body aches, loss of taste or smell, sore throat, congestion and nausea. Severe cases can lead to pneumonia, acute respiratory distress syndrome, organ failure and death.^[19]

PNEUMONIA

Pathogen

Streptococcus pneumoniae is a bacterium that can cause various infections, including pneumonia, meningitis and bacteremia.^[20]

Carriers and transmission

It spreads through respiratory droplets from coughs or sneezes. People can carry the bacteria in their noses and throats without showing symptoms and still spread it to others.

Symptoms and effects

Symptoms vary depending on the infection type. Pneumonia symptoms include fever, chills, cough, shortness of breath and chest pain.^[21]

With some diseases caused by viruses, some by bacterium and one even by *Plasmodium*. Immunoinformatics worked successfully in all cases and was key in highlighting regions of interest from amongst these pathogens.

Immunoinformatics tools have been instrumental in advancing vaccine development against a range of infectious diseases. For instance, in the context of the influenza virus, Ramírez-Salinas *et al.* (2020) designed hybrid peptides (P11 and P14) using NetMHC and ABCpred servers to identify conserved epitopes from hemagglutinin and neuraminidase proteins. These peptides showed high binding scores to multiple MHC-I and MHC-II alleles (NetMHC II scores >9.0 for human leukocyte antigen DR beta 1 ([HLA]-DRB1)1001 and NetMHC scores <0.12 for HLA-B3901). Structural stability was confirmed through molecular dynamics simulations over 500 ns, with P11 exhibiting the lowest root mean square deviation (RMSD) and radius of gyration (a measure of the molecule's structural compactness) values, indicating high stability. Experimentally, P11 and P14 induced high immunoglobulin G (IgG) antibody titres in rabbits (up to 1:800), and hemagglutination inhibition titres of 1:384 and 1:960, respectively. In addition, they demonstrated neutralising activity in mice with plaque reduction neutralisation test (PRNT₅₀) titres of 380 (P11) and 1600 (P14), supporting their potential as cross-reactive epitope vaccine candidates against diverse influenza strains.^[22] Similarly, in the fight against *malaria*, Atapour *et al.* (2022) employed an immunoinformatics pipeline targeting the plasmodium falciparum glutamic acid-rich protein (PfGARP) protein of *P. falciparum* to design a multi-epitope vaccine. Five high-scoring linear B-cell epitopes (e.g. 'HGEENLYEEMVSEINN' with a score of 0.93 from ABCpred) and five helper T lymphocyte (HTL) epitopes (e.g. 'ILNKSFDSITGRLLN' with a percentile rank of 11.35 and IC₅₀ of 1257 nM for HLA-DP) were selected. The final 414-amino acid construct was predicted to be antigenic with a VaxiJen score of 0.6976 and non-allergenic. Molecular docking with Toll-like receptor-5 (TLR-5) revealed strong binding affinity (-1353.6 kcal/mol), and molecular dynamics simulations showed structural stability with root mean square fluctuation values as low as 3.57 Å. *In silico* immune simulations

indicated robust immunogenicity, including IgM titres of ~530,000, combined IgG1 + IgG2 titres of ~150,000 and elevated levels of interferon-gamma (IFN- γ) and interleukin (IL-2), suggesting a strong humoral and cellular immune response.^[23] Furthermore, in TB research, Ning *et al.* (2023) proposed a multi-stage, multi-epitope subunit vaccine against *M. tuberculosis* using a comprehensive immunoinformatics framework. The final vaccine construct included 12 B-cell, 11 cytotoxic T lymphocyte (CTL) and 12 HTL epitopes, providing broad immune system coverage. Structural modelling confirmed a globular, stable and hydrophilic conformation with favourable thermostability, supporting its suitability for expression and formulation. Molecular docking demonstrated strong and stable interaction with the TLR-4 receptor, a key trigger of innate immunity. Immune simulations predicted the induction of robust cellular and humoral responses, indicating that the vaccine could elicit protective immunity across multiple stages of TB infection.^[24] Kaushik *et al.* (2022) used a robust immunoinformatics approach to design a cross-reactive, peptide-based multi-epitope vaccine targeting all four serotypes of the DENV 1–4. Out of 13,501 predicted MHC-II binding CD4+ epitopes, 10 conserved, non-toxic, IFN- γ -inducing peptides were identified. The final construct incorporated three of these epitopes and was predicted to be antigenic (VaxiJen score = 0.463), non-toxic and stable. Structural modelling and docking with TLR-5 showed strong interaction (HADDOCK score = -73.4 ± 4.1), and MD simulations confirmed stable complex formation over 100 ns. The vaccine construct exhibited good solubility and thermostability (aliphatic index = 88.19; half-life = 30 h *in vitro*). *In vivo* validation in rabbits showed high antibody titres detectable even at 1:520,000 dilution through enzyme-linked immunosorbent assay, indicating potent immunogenicity.^[25] Khamjan *et al.* (2023) developed a multi-epitope subunit vaccine targeting the conserved N protein of SARS-CoV-2 using immunoinformatics tools. The final construct included 11 B-cell, 6 MHC class I and 14 MHC class II epitopes, all confirmed as non-allergenic and non-toxic. The vaccine exhibited strong antigenicity (VaxiJen score = 0.5840, without adjuvant) and high global population coverage (MHC-I = 90.07%, MHC-II = 96%). Molecular docking with TLR-3 showed high affinity (HDOCK score = -398.38) with 11 hydrogen bonds and five electrostatic interactions. Molecular dynamics simulations confirmed structural stability with an eigenvalue of 3.66×10^6 and low RMSD. The construct showed excellent physicochemical properties, including molecular weight of 65.9 kDa, aliphatic index = 54.19 and codon adaptation index (CAI) = 0.92 after codon optimisation for *Escherichia coli* expression, supporting its suitability for downstream *in vitro* validation.^[26] Miao *et al.* (2023) evaluated the immunoinformatics-predicted fusion protein vaccine PiuA-PlyD4 against *S. pneumoniae*. The construct

exhibited a VaxiJen score of 0.684, was non-allergenic and showed strong structural reliability (Z-score = -9.63 ; ERRAT = 94.4). It included abundant B-cell and MHC-II binding epitopes, with strong binding predictions across five HLA-DRB1 alleles. Docking simulations showed significant interaction with both TLR-2 and TLR-4 (binding scores: -209.35 and -254.94 , respectively), supported by 11 and 18 hydrogen bonds. Immunisation of C57BL/6 mice elicited robust IgG titres (7.81×10^5) and subtype-specific responses (e.g. IgG1: 2.68×10^5). The vaccine inhibited bacterial adhesion to A549 cells (colony reduction from 10.8×10^3 to 3.7×10^3 colony forming unit [CFU]) and significantly reduced lung and nasal colonisation. Moreover, the survival rate against a lethal serotype 3 challenge was 50%, with notable cytokine elevation (e.g. IFN- γ = 303.7 pg/mL, IL-10 = 996.1 pg/mL and tumour necrosis factor- α = 693.1 pg/mL), indicating strong Th1, Th2 and Th17 activation.^[27]

These collective efforts showcase the critical role of immunoinformatics in accelerating vaccine research and development for a wide range of infectious diseases, allowing significant advancements in global health protection.

THE TOOLKIT FOR IMMUNOINFORMATICS

In the ever-changing field of immunoinformatics, refined tools and algorithms are indispensable for epitope prediction and vaccine design, driving advancements in immunological research. Table 2^[28-36] offers a comparative summary of prominent immunoinformatics tools, highlighting their specific applications and core features. VaxiJen is a widely used tool designed for antigenicity prediction, employing alignment-independent algorithms to assess the antigenic properties of proteins based on their physicochemical properties. It aids in antigen selection by identifying potential vaccine candidates with high antigenic scores.^[28] The IEDB serves as a comprehensive repository of epitope data, providing access to a vast collection of experimentally validated epitopes from various pathogens. Researchers utilise IEDB for epitope mapping, epitope prediction and immune response analysis, contributing significantly to our understanding of immunogenicity.^[29]

NetCTL 1.2 is a powerful tool for predicting CTL epitopes, integrating neural network-based algorithms to predict peptide binding to MHC class I molecules and proteasomal cleavage sites. It facilitates the identification of potential CTL epitopes for vaccine development against intracellular pathogens.^[30] PEP-FOLD is a computational tool utilised for protein structure prediction and epitope modelling, employing de novo folding algorithms to predict the three-dimensional structure of peptides. It aids in epitope design by providing insights into peptide conformation and antigenic determinants.^[31,32]

Table 1: Applications of immunoinformatics tools across infectious diseases.

Infectious disease	Tools used	Outcomes	Reference
Influenza virus	NetCTL, MHC binding prediction algorithms	Identification of conserved T-cell epitopes, development of broadly protective vaccines	Ramírez-Salinas <i>et al.</i> , ^[22]
Malaria	IEDB, PEP-FOLD	Identification of novel vaccine candidates, epitope-based vaccines targeting <i>Plasmodium</i> species	Atapour <i>et al.</i> , ^[23]
Tuberculosis	IEDB resources, MHC-I and II binding prediction	Identification of vaccine candidates, development of peptide-based and subunit vaccines	Ning <i>et al.</i> , ^[24]
Dengue fever	VaxiJen, BCEPred	Identification of antigenic targets, epitope-based vaccines against dengue virus serotypes	Kaushik <i>et al.</i> , ^[25]
COVID-19	Various immunoinformatics tools	Rapid identification of immunogenic peptides and epitopes on SARS-CoV-2	Khamjan <i>et al.</i> , ^[26]
Pneumonia	Immunoinformatics prediction, molecular docking	High antigenicity, structural stability and robust antibody response in vaccine candidate PiuA-PlyD4	Miao <i>et al.</i> , ^[27]

MHC: Major histocompatibility complex, IEDB: Immune epitope database, CTL: Cytotoxic T lymphocyte, PEP-FOLD: Peptide folding, BCE: B-cell epitope

Table 2: Comparison of key immunoinformatics tools and their features.

Tool	Purpose	Features	References
VaxiJen	Antigenicity prediction	Alignment-independent, physicochemical properties	Doytchinova <i>et al.</i> , ^[28]
IEDB	Epitope prediction and mapping	Comprehensive epitope database, immune response analysis	Vita <i>et al.</i> , ^[29]
NetCTL	CTL epitope prediction	Neural network-based, MHC-I binding, proteasomal cleavage	Larsen <i>et al.</i> , ^[30]
PEP-FOLD	Protein structure prediction	De novo folding, 3D structure prediction	Thevenet <i>et al.</i> , ^[31] and Rey <i>et al.</i> , ^[32]
BepiPred 2.0/3.0	B-cell epitope prediction	Hidden Markov models, antibody response prediction	Jespersen <i>et al.</i> , ^[33] and Clifford <i>et al.</i> , ^[34]
SVMTrip	T-cell epitope prediction	Support vector machine algorithms, TCR interactions	Yao <i>et al.</i> , ^[35]
IFNepitope	IFN- γ -inducing epitope prediction	Machine learning algorithms, IFN- γ production	Dhanda <i>et al.</i> , ^[36]

MHC: Major histocompatibility complex, IEDB: Immune epitope database, CTL: Cytotoxic T lymphocyte, TCR: T-cell receptor, IFN- γ : interferon-gamma, SVM: Support vector machine, PEP-FOLD: Peptide folding

BepiPred 2.0 is a machine learning-based tool specialised in predicting B-cell epitopes, utilising hidden Markov models to identify linear epitopes from protein sequences. Now, BepiPred 3.0 has been created as an upgrade which assists in epitope mapping and vaccine antigen design by predicting regions likely to induce antibody responses.^[33,34] SVMTrip is an algorithm used for predicting TCR epitopes, employing support vector machine-based algorithms to identify T-cell epitopes that bind to MHC molecules and interact with TCRs. It aids in the identification of potential T-cell epitopes for vaccine development against various pathogens.^[35] IFNepitope is a computational tool designed for predicting IFN- γ -inducing epitopes, leveraging machine learning algorithms to identify peptide sequences capable of eliciting IFN- γ production from T cells. It facilitates the

design of vaccines aimed at inducing cell-mediated immune responses.^[36]

Comparative analyses have shown that while tools such as VaxiJen and BepiPred are highly effective for specific tasks, their performance can vary based on the pathogen and epitope type being studied. Integration of these tools into larger immunoinformatics pipelines enhances their utility, allowing for comprehensive analyses that combine antigenicity prediction, epitope mapping and immune response modelling.

Case studies, such as the development of novel vaccines for emerging infectious diseases, demonstrate the practical impact of these tools. For instance, the use of NetCTL and IFNepitope in designing T-cell based vaccines has shown

promise in preclinical trials, highlighting their potential in tackling intracellular pathogens.

Emerging trends in the field include the incorporation of deep learning techniques, which offer improved predictive accuracy and the ability to analyse complex immunological data. In addition, efforts to standardise datasets and improve data quality are crucial for the reliability of these predictive models.

Collectively, these tools and algorithms play pivotal roles in epitope prediction, vaccine design and immunological research, offering valuable insights and accelerating advancements in the field of immunoinformatics. The continuous development and refinement of these tools, supported by robust community efforts and adherence to data standards, promise to drive future breakthroughs in vaccine development and immunotherapy.

In addition to the above, tools such as NetMHCpan (for pan-allelic MHC-I binding prediction), Discotope (for conformational B-cell epitope prediction using 3D structures) and ElliPro (which combines solvent accessibility and protrusion indices for structure-based epitope mapping) are also widely used in structural vaccinology and immunoinformatics pipelines. These tools offer enhanced predictive capabilities when integrated with structural modelling and docking frameworks.

ADVANTAGES AND LIMITATIONS

Immunoinformatics tools play a crucial role in the design of vaccines and the prediction of epitopes, providing numerous benefits while also posing specific limitations and challenges. These tools accelerate the selection of antigens by promptly identifying potential vaccine candidates with elevated antigenic scores. Moreover, they facilitate precise epitope prediction, simplifying the recognition of immunogenic peptides and antigenic determinants. Furthermore, immunoinformatics tools aid in the cost-effective design of vaccines by diminishing the requirement for labour-intensive and costly experimental assays through computational forecasts and modelling. Nevertheless, these tools encounter challenges regarding precision, as dependence on computational algorithms and models could result in erroneous positives or negatives in epitope prediction. Data quality remains a critical challenge in immunoinformatics, particularly when relying on predicted epitopes or low-confidence protein annotations. To address this, researchers increasingly utilise curated databases such as IEDB, which provide experimentally validated epitope records. Preprocessing steps – such as filtering out transmembrane regions and signal peptides using tools such as transmembrane hidden markov model (TMHMM) and SignalP – help eliminate non-immunogenic sequences. In

addition, cross-validation of results using multiple prediction algorithms (e.g. NetCTL, NetMHCIIpan and VaxiJen) enhances the reliability of identified epitopes. Structural validation using 3D modelling and molecular docking further supports the biological plausibility of predictions. Emerging approaches also integrate machine learning ensembles that combine sequence-based, structural and antigenicity features to improve robustness against noise and variability in input data. In addition, computational resource demands may present obstacles, particularly for resource-intensive algorithms and simulations. In the domain of *in silico* vaccine design, constraints encompass numerous critical challenges that necessitate attention for real-world application. Challenges in accuracy persist in projecting immune responses solely based on computational models, with potential inaccuracies in protein modelling leading to errors in epitope recognition and vaccine design. Furthermore, despite progress in computational methodologies, experimental validation remains imperative to validate the effectiveness and safety of *in silico*-designed vaccines. The scarcity of diverse modelling approaches limits the range and adaptability of vaccine development strategies. Moreover, translating *in silico* projections into *in vivo* or *in vitro* settings poses a substantial hindrance, causing the need for further investigation to bridge this divide and enhance the pragmatic applicability of *in silico* vaccine design approaches.

FUTURE DIRECTIONS

In spite of obstacles such as problems with precision, issues with data quality and the requirement for experimental validation, immunoinformatics has made great strides. To overcome these obstacles and advance the area, future research efforts should give priority to improving computational models, optimising data fusion and refining experimental validation methods. Furthermore, exploring novel algorithms, expanding immunoinformatics applications and fostering interdisciplinary collaborations will support immunoinformatics' continuous progress, guaranteeing further breakthroughs in preserving world healthcare.

Moving forward, addressing challenges such as epitope variability, limited cross-protection, and reliance on *in silico* predictions will require integrative approaches. Incorporating population-specific HLA distribution data can improve epitope relevance in diverse regions. Combining immunoinformatics with artificial intelligence-driven learning frameworks and wet-lab validation pipelines will bridge the gap between prediction and real-world efficacy. Establishing global, open-access repositories for immunogenic peptide data, including failed predictions, can further enhance tool training and benchmarking. Finally, expanding immunoinformatics to include host-pathogen

co-evolution and immunodominance modelling may unlock new avenues for universal vaccine design.

CONCLUSION

To sum up, immunoinformatics has become a disruptive field at the nexus of immunology and computational biology, revolutionising the design of vaccines and the identification of epitopes. Immunoinformatics accelerates the process of creating vaccines against infectious diseases, particularly recently discovered pathogens like SARS-CoV-2, by combining genomes, proteomics and machine learning. By making antigen selection, epitope prediction and vaccine design simpler, the use of state-of-the-art tools and algorithms such as VaxiJen, IEDB, NetCTL, PEP-FOLD, BepiPred 3.0, SVMTrip and IFNepitope improves the efficacy and efficiency of immunological studies. Moreover, immunoinformatics exhibits flexibility in addressing a range of infectious diseases, permitting prompt reactions to new health risks and supporting the development of vaccines with extensive protection potential.

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