International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

The current potential for nucleoside analogues in preclinical stages as treatments for dengue virus: a protocol for systematic review

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ADMINISTRATIVE INFORMATION

Support - College of Medicine and Public Health, Advanced Studies Program.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 October 2025 and was last updated on 30 October 2025.

INTRODUCTION

Review question / Objective The aim of this study is to review and assess the published preclinical data on the efficacy of nucleoside analogues against dengue virus, to help guide efforts in potentially revisiting this class of compounds or optimise research efforts in other classes.

Rationale Dengue is a mosquito-borne viral disease particularly prevalent in tropical and subtropical climates. With an estimated 390 million dengue infections per year, dengue virus (DENV) presents a high health burden. Despite this, there are no clinically approved antivirals for treatment of dengue.

One category of antiviral candidates that was thought to be promising, is nucleoside analogues targeting viral replication machinery. This stems from successes of nucleoside analogues in treatment of hepatitis C virus; a virus closely related to dengue virus, and HIV. Multiple anti-dengue virus compounds have been previously identified to show in vitro or in vivo efficacy but did not progress to further clinical studies due to reasons such as toxicity, lack of efficacy in clinical trials, and lack of funding. In recent years, another category of compounds targeting NS3-NS4B viral protein interactions have emerged as the centre of attention in anti-DENV research, with compounds such as mosnodenvir (JNJ-1802) and NITD-688 showing pan-serotype activity and excellent antiviral potential in pre-clinical trials. These have progressed to clinical trials, with NITD-688 currently recruiting but mosnodenvir clinical trials terminated due to commercial decisions.

With these new NS3-NS4B-targeting agents taking the lead as dengue antivirals, it raises the question whether we have overlooked the true potential of nucleoside analogues as dengue antiviral agents. Hence, there is a need to review the antiviral potential of current nucleoside analogues against dengue virus and compare this potential to current

NS3-NS4B inhibitors. This involves investigating and comparing preclinical models and data and linking this to outcomes of clinical trials, but not specifically interrogating clinical trials data.
We have rationalised to focus on NS3-NS4B inhibitors (JNJ-1802 or JNJ-A07 and NITD-688) and nucleoside analogues (balapiravir, AT-752, NITD-008 and 2-methylcytosine or derivates) as the most promising nucleoside analogues from past data. Additionally, any novel nucleoside analogues, published since 2020, will be captured with our search terms.

Condition being studied Dengue virus is a significant global cause of disease ranging from dengue fever to more severe dengue with the potential for life-threatening haemorrhagic disease. This is of growing incidence and expanding geographic distribution.

METHODS

Search strategy Literature searches will be undertaken in electronic databases including PubMed, Embase, Web of Science, Scopus for studies published from January 2020 onwards.
Combinations of search terms 'dengue', 'DENV', 'nucleoside analogue*', 'nucleoside inhibitor', and 'antiviral' will be used, as well as searches including previously significant nucleoside analogues for a broader background search for information:
- (dengue OR DENV) AND ((nucleoside OR nucleotide OR adenosine OR cytidine OR guanosine OR uridine) AND (analogue* OR inhibitor))
- (dengue OR DENV) AND (balapiravir OR "AT-752" OR "NITD-008" OR "2'-C-methylcytidine*")
Additionally, there will be a search using the following terms for NS3-NS4B inhibitors to compare the outcomes against nucleoside inhibitors:
- (dengue OR DENV) AND ("NS3-NS4B inhibitor" OR "JNJ-1802" OR mosnodenvir OR "JNJ-A07" OR "NITD-688" OR "EYU-688")
Searches in ClinicalTrials.gov will also be conducted to obtain a background overview of current clinical trials for nucleoside analogues using combinations of the same search terms.

Participant or population Not applicable, pre-clinical data from in vivo laboratory animals such as mice.

Intervention Dengue infection in vitro or in vivo, with or without antiviral nucleoside analogue treatment. Treatment may be pre or post viral infection.

Comparator NS3-NS4B treatment in preclinical studies as for the intervention.

Study designs to be included in vitro and in vivo studies, with treatment added pre or post viral infection.

Eligibility criteria This review will include studies of nucleoside analogues with published preclinical data of either in vitro or in vivo animal models with EC50 values. To reflect current research efforts, only studies published from January 2020 up to the search date will be included.
We will also limit to peer reviewed publications available in the English language
Studies will be excluded that have been retracted or contain evidence of bias or conflict of interest.

Information sources Electronic databases as defined in the search strategy, clinical trial registers. Grey literature will not be considered.

Main outcome(s) A spreadsheet document will be used to record relevant extracted data. One author will extract the following data:
- Preclinical model(s) of the study, including animal strain or cell type studied if in vitro
- EC50 of the nucleoside analogue
- Viral replication data
- Protection from infection

Main outcomes will be comparison of EC50 values and antiviral activity in different cell types
In vivo models will include outcomes comparing measures of viraemia and protection from disease.

Additional outcome(s) Additional outcomes will interrogate the data interpretation for efficacy and rationale for future applications as antiviral agents with potential.
Pre-clinical efficacy will also be related to any future progression and benefits in clinical trials as assessed by analysis of the clinical trials register.

Data management Publications from all searches will be managed via Covidence systematic review management software to remove duplicates and share amongst the three authors.
The authors will independently screen the titles and abstracts of the publications to identify relevant literature against the outcome. One author will then review the full text to assess eligibility for inclusion by using the Critical Appraisal Skills Programme checklist, and confirmation of inclusion will be discussed with at least one other author. Any disagreements will be resolved through discussion of the text, and another author will be consulted in case a consensus cannot be reached.

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A spreadsheet such as an excel document will be used to record relevant extracted data.

Quality assessment / Risk of bias analysis Risk of bias will be assessed by a Critical Appraisal Skills Programme checklist, modified with the following headings, and applied for each selected publication:
- Are the results of the study valid
- What are the results
- Are there any confounders.

Strategy of data synthesis Data will be qualitatively compared across and within comparable platforms, but will not be combined and reassessed.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction English language only will be considered.

Country(ies) involved Australia.

Keywords Dengue; nucleoside analogue; antiviral.

Dissemination plans Generation of a manuscript and publication in peer reviewed journal.

Contributions of each author
Author 1 - Jaehee Jang - Co-designed study protocol; Undertake Search strategy; reviewed manuscripts and data extraction; Data management; drafted and edited manuscript.
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