A Manuscript Microscope 'Sentence Audit' of:

Predicting potentially permissive substitutions that improve the fitness of A(H1N1)pdm09 viruses bearing the H275Y NA substitution

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The Manuscript Microscope Sentence Audit is a research paper introspection system that parses the text of your manuscript into minimal sentence components for faster, more accurate, enhanced proofreading.

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Manuscript Source: https://www.biorxiv.org/content/10.1101/2021.03.21.436293v1

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Audit Date: 31/03/21 **Audit Identifier:** TOWT8NSE9K342KY **Code Version:** 3.6

Features of the Sentence Audit:

The Sentence Audit combines two complementary proofreading approaches:

1. Each sentence of your text is parsed and displayed in isolation for focused inspection.
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The Minimal Sentence Components shown are the smallest coherent elements of each sentence of your text as derived from it's conjunctions, prepositions and selected punctuation symbols (i.e. commas, semicolons, round and square brackets).

The combined approaches ensure easier, faster, more effective proofreading.

Comments and Caveats:

• The sentence parsing is achieved using a prototype natural language processing pipeline written in Python and may include occasional errors in sentence segmentation.

• Depending on the source of the input text, the Sentence Audit may contain occasional html artefacts that are parsed as sentences (E.g. "Download figure. Open in new tab").

• Always consult the original research paper as the true reference source for the text.

Contact Information:

To get a Manuscript Microscope Sentence Audit of any other research paper, simply forward any copy of the text to John.James@OxfordResearchServices.com.

All queries, feedback or suggestions are also very welcome.

Research Paper Sections:

The sections of the research paper input text parsed in this audit.

Section No.	Headings	Sentences
Section: 1	Abstract	12
Section: 2	1. Introduction	15
N/A	--- --- --- --- --- --- ---	0
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The Sentence Audit Of The Research Paper

Title # Predicting potentially permissive substitutions that improve the fitness of A(H1N1)pdm09 viruses bearing the H275Y NA substitution

S1 [001] Abstract

S1 [002] Oseltamivir-resistant influenza viruses arise due to amino-acid mutations in key residues, but these changes often reduce their replicative and transmission fitness.

Oseltamivir-resistant influenza viruses arise ...
... due to amino-acid mutations ...
... in key residues, ...
... but these changes often reduce their replicative ...
... and transmission fitness.

S1 [003] Widespread oseltamivir-resistance has not yet been observed in A(H1N1)pdm09 viruses.

Widespread oseltamivir-resistance has not ...
... yet been observed ...
... in A(H1N1)pdm09 viruses.

S1 [004] However, it is known that permissive mutations in the neuraminidase (NA) of former seasonal A(H1N1) viruses from 2007-2009 buffered the detrimental effect of the NA H275Y mutation, resulting in fit oseltamivir-resistant viruses that circulated widely.

However, ...
... it is known ...
... that permissive mutations ...
... in the neuraminidase ...
... (NA) ...
... of former seasonal A(H1N1) ...
... viruses ...
... from 2007-2009 buffered the detrimental effect ...
... of the NA H275Y mutation, ...
... resulting ...
... in fit oseltamivir-resistant viruses ...
... that circulated widely.

S1 [005] This study explored two approaches to predict permissive mutations that may enable a fit H275Y A(H1N1)pdm09 variant to arise.

This study explored two approaches ...
... to predict permissive mutations ...
... that ...
... may enable a fit H275Y A(H1N1)pdm09 variant ...
... to arise.

S1 [006] A computational approach used phylogenetic and in silico protein stability analyses to predict potentially permissive mutations, which were then evaluated by in vitro NA enzyme activity and expression analysis, followed by in vitro replication.

A computational approach used phylogenetic ...
... and in silico protein stability analyses ...
... to predict potentially permissive mutations, ...
... which were then evaluated ...
... by in vitro NA enzyme activity ...
... and expression analysis, ...
... followed by in vitro replication.

S1 [007] The second approach involved the generation of a virus library which encompassed all possible individual 2.9 × 104 codon mutations in the NA whilst keeping H275Y fixed.

The second approach involved the generation ...
... of a virus library ...
... which encompassed all possible individual 2.9 × 104 codon mutations ...
... in the NA whilst keeping H275Y fixed.

S1 [008] To select for variant viruses with the greatest fitness, the virus library was serially passaged in ferrets (via contact and aerosol transmission) and resultant viruses were deep sequenced.

To select ...
... for variant viruses ...
... with the greatest fitness, ...
... the virus library was serially passaged ...
... in ferrets ...
... (via contact ...
... and aerosol transmission) ...
... and resultant viruses were deep sequenced.

S1 [009] The computational approach predicted three NA permissive mutations, and even though they only offset the in vitro impact of H275Y on NA enzyme expression by 10%, they could restore replication fitness of the H275Y variant in A549 cells.

The computational approach predicted three NA permissive mutations, ...
... and even though they ...
... only offset the in vitro impact ...
... of H275Y ...
... on NA enzyme expression ...
... by 10%, ...
... they could restore replication fitness ...
... of the H275Y variant ...
... in A549 cells.

S1 [010] In our experimental approach, a diverse virus library (97% of 8911 possible single amino-acid substitutions were sampled) was successfully transmitted through ferrets, and sequence analysis of resulting virus pools in nasal washes identified three mutations that improved virus transmissibility.

In our experimental approach, ...
... a diverse virus library ...

... (97% ...
... of 8911 possible single amino-acid substitutions were sampled) ...
... was successfully transmitted ...
... through ferrets, ...
... and sequence analysis ...
... of resulting virus pools ...
... in nasal washes identified three mutations ...
... that improved virus transmissibility.

S1 [011] Of these, one NA mutation, I188T, has been increasing in frequency since 2017 and is now present in 90% of all circulating A(H1N1)pdm09 viruses.

Of these, ...
... one NA mutation, ...
... I188T, ...
... has been increasing ...
... in frequency ...
... since 2017 ...
... and is now present ...
... in 90% ...
... of all circulating A(H1N1)pdm09 viruses.

S1 [012] Overall, this study provides valuable insights into the evolution of the influenza NA protein and identified several mutations that may potentially facilitate the emergence of a fit H275Y A(H1N1)pdm09 variant.

Overall, ...
... this study provides valuable insights ...
... into the evolution ...
... of the influenza NA protein ...
... and identified several mutations ...
... that ...
... may potentially facilitate the emergence ...
... of a fit H275Y A(H1N1)pdm09 variant.

S2 [013] 1. Introduction

S2 [014] Oseltamivir is a neuraminidase inhibitor (NAI) which is widely used and prescribed for the treatment of influenza, and is often stockpiled for pandemic purposes [1-5].

Oseltamivir is a neuraminidase inhibitor ...
... (NAI) ...
... which is widely used ...
... and prescribed ...
... for the treatment ...
... of influenza, ...
... and is often stockpiled ...
... for pandemic purposes ...
... [1-5].

S2 [015] This drug was designed to target the conserved active site of the influenza virus neuraminidase (NA) glycoprotein and inhibit its enzymatic function, hence reducing the capacity of virus to release from infected host cells [6, 7].

This drug was designed ...
... to target the conserved active site ...
... of the influenza virus neuraminidase ...
... (NA) ...
... glycoprotein ...
... and inhibit its enzymatic function, ...
... hence reducing the capacity ...
... of virus ...
... to release ...
... from infected host cells ...
... [6, 7]...
... .

S2 [016] However, amino acid substitutions that arise in the drug binding region of the NA glycoprotein can reduce virus susceptibility to oseltamivir [8, 9].

However, ...
... amino acid substitutions ...
... that arise ...
... in the drug binding region ...
... of the NA glycoprotein can reduce virus susceptibility ...
... to oseltamivir ...
... [8, 9]...
... .

S2 [017] For example, the H275Y amino acid substitution that is commonly reported in the NA of influenza A(H1N1) viruses [1-4,10, 11] prevents the conformational change of the E276 amino acid which normally creates a hydrophobic pocket necessary for oseltamivir binding, and leads to reduced oseltamivir susceptibility [12-15].

For example, ...
... the H275Y amino acid substitution ...
... that is commonly reported ...
... in the NA ...
... of influenza A(H1N1) ...
... viruses ...
... [1-4,10, 11]...
... prevents the conformational change ...
... of the E276 amino acid ...
... which normally creates a hydrophobic pocket necessary ...
... for oseltamivir binding, ...
... and leads ...
... to reduced oseltamivir susceptibility ...
... [12-15].

S2 [018] Therefore, the emergence of viruses bearing this substitution is of particular concern.

Therefore, ...
... the emergence ...
... of viruses bearing this substitution is ...

End of Sample Audit

This is a truncated Manuscript Microscope Sample Audit.

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