

## MEMORANDUM

<b>From:</b>	Director, NTD	<b>To:</b>	Director, HPS	<b>Date:</b>	21 May 2021
<b>Our ref:</b>		<b>Attention:</b>			
<b>Your ref:</b>		<b>Through:</b>			
<b>Originator:</b>		<b>Subject:</b>	Meeting of the 23 <sup>rd</sup> Expert Committee on selection and use of essential medicines		

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Thank you very much for the memo sent to our department regarding the application for the above meeting. As technical lead department for dengue we have circulated the submission on the potential addition of dengue-induced acute liver failure as an indication for N-acetylcysteine (NAC) in the EML and EMLc, obtaining a number of expert reviews.

From our perspective the overall conclusions are:

The evidence presented by the authors for the incorporation of NAC in dengue associated liver injury/failure is based on incomplete reports. Further studies are needed to strengthen the evidence base.

It must be very clear that including NAC as an essential medicine does not represent a recommendation for its use in dengue-induced liver failure.

We do not have any objection to including NAC as an essential medicine for liver failure in general if there are sufficient data in the relevant submission.

We enclose the additional opinion of the PAHO International Arbovirus Task Force.

Thank you very much again for the opportunity to review this document.

Dr Mwelecele Ntuli Malecela

## Approval for eDocument - HQ-2021-DOCS-eMemo-86654

Action	Action Taken By	Received On(UTC)	Action Taken On(UTC)	Comments	Attachments
Submitted	AIME-MCDONALD , Elizabeth (Linda)	NA	21-May-2021 4:00 PM		
Approved & Re-Assigned	MALECELA, Mwelecele Ntuli	21-May-2021 4:02 PM	24-May-2021 11:15 AM	Re-Assigned To:ONDARI, Clive Comments: Dear Clive. Please find the attached memo for your attention	
Cleared	ONDARI, Clive	24-May-2021 11:16 AM	24-May-2021 3:26 PM		
Approved	HUTTNER, Benedikt	25-May-2021 7:01 AM	25-May-2021 7:06 AM		
Approved	ONDARI, Clive	24-May-2021 3:33 PM	25-May-2021 8:33 AM		

## PAHO TECHNICAL REVIEW OF DOCUMENT

### Acetylcysteine (N-acetylcysteine, NAC) for the management of non-acetaminophen-induced acute liver failure

The document was shared with the PAHO International Arbovirus Task Force (PAHO International GT-Arbovirus), who made a technical review of the contents.

There are several aspects that PAHO International GT-Arbovirus highlighted in the document:

- Regardless of the great effort to develop this document, none of the studies included in it were a clinical trial nor prospective cohorts, but retrospective studies, case report or case series. So, the scientific evidence is not the optimal.
- In the Americas, we do not see a high incidence of liver failure in dengue cases, as described in the document even with 63% of cases with liver failure. It is well known that flavivirus (includes dengue virus) have an affinity to affect the liver. In “our” dengue (in the Americas), even when it is extremely common for patients to increase transaminases, but in most of the cases only reaches up to a few hundred U / L and everything resolves with rest in a few days or weeks. Exceptionally, it exceeds 1000 IUs, although several of us (physicians) have had cases with more than 10,000, with spontaneous recovery when well managed.
- In the Americas, complicated cases of dengue, included those with liver failure, are managed in Intensive Care Units (ICU). ICU have their own protocols to manage the patients.
- On the other hand, it is difficult to distinguish in many dengue cases if the liver damage is a sum of factors such as the virus itself, use of acetaminophen, or shock. In case the liver failure is due to acetaminophen, patients could benefit with the use of NAC.

The PAHO International GT-Arbovirus is not doing a recommendation, but only sharing their expert opinion of the document. In our PAHO dengue guidelines, the management of complicated cases with organ failure is not included. These complicated cases are managed in ICU according to national ICU protocols. For this reason, NAC is not included in our guidelines. It must be very clear that including NAC as an essential medicine does not represent a recommendation for its use in severe dengue cases (liver failure). We do not oppose to include it as essential medicine, but in order to be recommended for use (as part as clinical guidelines) we need to follow GRADE methodology recommended by WHO and PAHO.