THE GAMBIA

CAUSALITY ASSESSMENT REPORT ON ACUTE KIDNEY INJURY OUTBREAK IN CHILDREN

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GLOSSARY OF TERMS

ADR	Adverse drug reaction
2-HEAA	2-hydroxyethoxyacetic acid
AKI	Acute Kidney Injury
AWD	Acute watery diarrhea
CAC	Causality Assessment Committee
CFR	Crude Fatality Rate
DEG	Diethylene glycol
DGA	Diglycolic acid
EDC	Epidemiological and Disease Control
EFSTH	Edward Francis Small Teaching Hospital
EG	Ethylene glycol
IQR	Interquartile range
MCA	Medicines Control Agency
µmol/l	Micromole per litre
mmol/l	Millimole per litre
MoH	Ministry of Health
WHO	World Health Organization

EXECUTIVE SUMMARY

An outbreak of cases of Acute Kidney Injury (AKI) among children was detected in Gambia on 26th July, 2022. Diethylene glycol (DEG) and ethylene glycol (EG) were detected in samples of medicines analyzed in Ghana, France and Switzerland and led to withdrawal of many paediatric medicines from the market. A Causality Assessment Committee (CAC) was set up by the Gambian Ministry of Health.

The Epidemiology and Disease Control (EDC) unit in the Gambia reported and line listed 82 children that had AKI. Thirteen cases were not evaluated because data of these cases were not provided to the CAC. The remaining 69 cases were assessed by the CAC (including 62 deaths). Of these cases, 13 were excluded because 10 had insufficient data and 3 did not meet the case definition, leaving 56 cases for in depth-assessment.

Twenty-two (22) cases were assessed as very likely to have died due to diethylene glycol (DEG) and ethylene glycol (EG) poisoning from the analyzed oral liquid formulations. For the remaining 34, there were 30 suspected poisoning cases with no other cause of AKI and incomplete evidence for the ingestion of a medicinal product containing the poison (DEG & EG). They were assessed to have a suspected poisoning but of an uncertain or unknown exposure. Two of the patients in this group also had autopsy that confirmed renal and hepatic pathological findings consistent with features of DEG/EG poisoning. The 4 remaining cases had possible alternative/contributing diagnosis and incomplete evidence for the ingestion of a medicinal product containing the poison (DEG & EG). The sudden cessation of AKI cases following the recall of syrups with the toxic medicinal products by the Government coincided with the termination of the outbreak since the 5th October 2022. This can be interpreted as a "dechallenge" at the population level and is highly suggestive that the 30 children also died due to severe DEG/EG poisoning just like the 22 cases. As of 9th December 2022, no further cases of AKI have been detected.

The toxic substances DEG and EG were detected in four medicinal products ingested by the children. The products were all manufactured by one pharmaceutical company and have been withdrawn from the market. There are some laboratory analyses currently pending (**cases will be reassessed once results are available**) and no toxic substances have been detected in medicinal products supplied by other pharmaceutical companies in The Gambia. No signs of any other outbreak (such as an infectious agent) than the poisonings were detected.

There is thus a need to educate the public/parents, and healthcare professionals about the appropriate use of medicines especially buying medications without consulting a medical practitioner for prescription.

Finally, accept our sincere condolences for this tragic event and we say "*Never Again*".

INTRODUCTION

This is the first time that an AKI epidemic is reported in Gambia. In July 2022 an unusual increase in the cases of severe acute kidney injury (AKI) often resulting in the death of the children was noted in Gambia. Using retrospective data collection and prospective surveillance the Epidemiology and Disease Control (EDC) Unit of the Gambia identified a cohort of 82 children with AKI during June to October 2022 outbreak .

Diethylene glycol (DEG) and ethylene glycol (EG) poisoning through contaminated medicines was suspected in the differential diagnosis as cause of AKI given previous reports of outbreaks of AKI in children due to these toxic substances (A Abubakar et al, 2009). Based on this investigation 38 medicines taken by the children were sent for independent analysis to three (3) countries namely; Nine (9) samples (first batch) were taken to United States Pharmacopeia laboratory Ghana. However, a second batch of 15 samples were also sent to same laboratory in Ghana. Another, 9 samples were sent to Centre Humanitaire Des Metiers De La Pharmacie (CHM) France and 23 samples to Itertek (Schweitz) AG, Switzerland. Toxic concentrations of DEG/EG were identified in four (4) products and all were from the same manufacturer. One product was independently confirmed by all laboratories and the remaining 3 products were tested and confirmed to have toxic concentrations of DEG/EG by Itertek (Schweitz) AG, Switzerland (see annex for details including batch numbers).

The contaminated products were all manufactured by one pharmaceutical company and have been withdrawn from the community and the market. There are some laboratory analyses currently pending for 108 syrups and no toxic substances have been detected in medicinal products taken by the children that were supplied by other pharmaceutical companies in The Gambia.

In order to assess the cause of the outbreak of AKI in children in Gambia and the potential link to DEG / EG poisoning a causality assessment procedure was initiated by convening a Causality Assessment Committee (CAC) consisting of national and international experts in Senegambia hotel from December 5 to 9, 2022.

Clinical Toxicology of DEG

Diethylene glycol (DEG) and ethylene glycol (EG) are organic compounds found in certain consumer products, such as antifreeze, industrial solvent and as raw material for the manufacturing of polymers. Intentional and accidental ingestion of DEG-containing products has produced poisoning infrequently in the US (Marraffa et al., 2008), but infamous epidemic poisoning has occurred when it is used as an illegal replacement for glycerine or propylene glycol as solvent in medications, as of 2008 (Alkahtani et al., 2010).

Since 1937 there have been several epidemics globally where predominantly young children have presented with an acute onset of acute kidney injury after ingestion of medicines contaminated with DEG and / or EG, notably in Bangladesh (Hanif M et al., 1995), Haiti (O'Brien et al., 1998), and Nigeria (A Abubukar et al., 2009).

In these cases, more expensive, but significantly less toxic, glycols or glycerine had been substituted knowingly or inadvertently in pharmaceutical preparations with DEG and / or EG. DEG / EG poisoning due to contaminated medicines is associated with high case fatality rates and over 300 deaths have been reported in the literature in the context of outbreaks, but this is certainly an underestimation.

The hallmark of DEG poisoning is acute kidney injury (AKI) caused by proximal tubule cell necrosis. AKI is the main cause of death in DEG poisoning, but symptoms are wide ranging and also include gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) and neurological symptoms (headache, altered mental status). (O'Brien et al., 1998). The exact mechanism of toxicity of EG and DEG remains unclear. For DEG renal toxicity is thought to be mediated mostly by accumulation of its metabolite 2-hydroxyethoxyacetaldehyde in the kidney (Besenhofer et al., 2010, 2011, Landry et al., 2011), but the parent compound is also considered toxic as well. AKI is reported to occur rapidly, i.e. 8 to 24 hours after exposure to lethal doses of diethylene glycol (in adults estimated to be around 1ml per kg of body weight).The severity of symptoms depends on the cumulative dose.

There are no specific laboratory markers for EG / DEG poisoning (detection of EG/DEG in blood and other body fluids is often not feasible). A complicating factor when assessing the possibility of DEG / EG poisoning through contaminated medicines is the fact that these medicines are usually taken to treat some symptoms or a disease, e.g., fever, cough, loose stools, vomiting caused by viral respiratory or gastrointestinal infections. The symptoms of the underlying disease may at least initially be similar to those of the poisoning. The diagnosis of DEG / EG poisoning is usually clinical in the context of a compatible clinical presentation, absence of an alternative diagnosis and exposure to EG / DEG.

As mentioned above measurement of DEG & EG concentration in human tissues is not used to confirm or assess the severity of poisoning. The diagnosis of a poisoning by DEG & EG is based on information of the intake of the toxic substance and symptoms characteristically associated with it. For determination of severity of the poisoning the Poison Severity Score (PSS) is usually used (Persson H.E et. all 1998). Hence, re-challenge in suspected DEG & EG poisoning is not feasible even if there had been survivals, as substance suspected as the cause of death is toxic.

Clinical Epidemiology

On the 26th of July 2022, the Epidemiology and Disease Control (EDC) Unit received a report through the Director of Health Services from a paediatric nephrologist indicating a sudden increase in the number of cases of Acute Kidney Injury (AKI) among children aged 2 months to 8 years being treated at the Edward Francis Small Teaching Hospital (EFSTH) in Banjul.

A case definition was developed by EDC and adopted for active case searching. The first case was retrospectively traced to 27th of June 2022. The last confirmed case was seen on 5th of October 2022 with no additional cases after that. As of 5th December 2022, 69 confirmed cases of AKI with 62 deaths (CFR 90 %) were assessed by the Causality Assessment Committee (CAC). .

Of note was that as of 6th October 2022 some paediatric syrups were withdrawn based on the suspicion of contaminated medicines being a potential cause of the AKI outbreak and that, 4 out of 38 syrups were confirmed to contain DEG & EG. The contaminated products were mostly obtained over the counter without medical consultation and dispensed at pharmacy outlets within the communities.

AIM AND OBJECTIVES

1. **AIM :**
   To carry out a causality assessment on the AKI victims in The Gambia
2. **SPECIFIC OBJECTIVES:**
   A. To ascertain the causal association or risk factors for the morbidity and mortality in the AKI victims
   B. To summarize the final points for communication to Gambians on the cause of the AKI by the Hon. Minister of Health

METHOD FOR THE CAUSALITY ASSESSMENT

The entire epidemic led to various data collection processes. When the alert of a possible outbreak was detected, active data collection and case identification started. A case definition was developed, a case report form was elaborated and clinical medical folders were reviewed supplemented by interviews with caregivers for identified AKI cases.

DATA COLLECTION

As soon as the alert of a possible outbreak was detected, the EDC started active data collection and case identification. A case definition was developed and all cases that met the criterion were captured on the Adverse Drug Reaction (ADR) form (see annexure). As of December 5, 2022 Eighty-two (82) confirmed AKI cases (including 70 deaths) had been collected in a line list by EDC of which 69 were provided to the CAC for assessment.

The EDC line list was used by the MCA, MoH and the EFSTH to conduct AKI case investigation audit to the parents and caregivers of the children to know the batch number, brand and generic names of the oral formulations ingested by the children. The listed names of the liquid formulations with respect to the pharmacy and drug stores where the medicines were purchased led to a field work that helped in obtaining names of the medicines. Five (5) children were referred to Senegal for further management and the details of their treatment and outcome were obtained and assessed.

The clinical folders and laboratory investigations carried out at the EFSTH as the only tertiary institution with nephrology facility were retrieved and carefully studied. In addition, information of the laboratory determinations of DEG and EG in the medicines that were suspected to have possibly contained toxic ingredients were considered in the analysis to arrive at the causal associations. A modification of the French method for the Causality Assessment of Adverse Drug Reactions like the updating method (Yannick Arimone et. al) were applied on each case. The modification was necessary as the options to determine strong causality, DE-challenge (disappearance/reduction of symptoms after withdrawal of the suspected treatment) and Re-challenge (return of symptoms when treatment is reintroduced) could not be used as the children had all died.

The causality assessment was conducted between December 5 and 9, 2022 at the Salon Amina conference hall of Senegambia Hotel.

The core members nominated a chairman for the CAC and they unanimously decided to adopt the Modified French Method of the Causality Assessment of Adverse Drug Reaction. The summary of this method is attached as annexure.

A daily attendance list was recorded for the core members and observers from Ministry of health and other developmental health partners and is in safe keep with the MCA. The secretariat was constituted by the MCA which also presented all the necessary legally binding documents (agenda, attendance sheet, confidentiality and impartiality forms) and are attached as annexure.

RESULTS FOR THE CAUSALITY ASSESSMENT

The demographic and clinical characteristics of the AKI cases

The committee assessed 69 cases (13 cases were not assessed because 3 cases did not meet the AKI case definition while, 10 cases had insufficient data). [See flowchart and table 1]. In-depth assessment of the remaining 56 cases revealed a median age of 19 months (IQR 10.5-27 months). The majority of the cases were male 37/56 (66.1%). The most common clinical findings at presentation were fever 54/56 (96.4%) vomiting 52/56 (92.9%) and oliguria/anuria 51/56 (91.1%). The median values of urea and creatinine for these cases at presentation were 28.5 (IQR 19-39.7) mmol/l and

702.3 (IQR 568-896.7) µmol/l, respectively. Overall mortality was 56/56 (100 %) and the median duration of hospital admission was 4 (IQR 1 – 5) days. Out of the 56 cases, 22 were assessed as likely to have been exposed to DEG and EG from the analyzed oral liquid formulations while, 34 cases were assessed to have an unknown or uncertain exposure.

Table 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF AKI CASES

Variable	**n=56 (100%)**
Age (months)	
Mean	22.6
Median (IQR)	19 (10.5-27)
Sex	
Male	37 (66.1)
Female	19 (33.9)
Symptoms	
Fever	54 (96.4)
Vomiting	52 (92.9)
Oliguria/anuria	51 (91.1)
Loose stools	25 (44.6)
Cough	20 (35.7)
Duration of admission: Median (IQR) days	4 (1-5)
	n=43
Urea at admission: Median (IQR) mmol/l	28.5 (19-39.7)
	n=46
Creatinine at admission: Median (IQR) umol/l	702.3 (568-896.7)
Total short term mortality	56 (100)

Clinical characteristics of cases with likely exposure to DEG and EG

Twenty-two (22) of 56 cases (39.3%) were assessed as having exposure to medications contaminated with DEG/EG and no other cause of AKI was identified after an in-depth review (Table 2) meaning that, they had AKI and died [22/22 (100%)]. Their death can be attributed with high certainty to DEG & EG poisoning. The majority 13/22 (59.6%) were male and the median age was 20 (IQR 11-27) months. The most common clinical findings at presentation were oliguria/anuria 22/22 (100%) fever 21/22 (95.5) and vomiting 21/22 (95.5). The Median values of urea and creatinine for these cases at presentation were as follows; 29.8 (IQR 16.7-39.9) mmol/l and 746 (IQR 666.7-905.9) µmol/l, respectively. Overall mortality was 22/22 (100%) and the median duration of admission was 3 (IQR 1 – 5) days. The median percentage concentration of DEG and EG in the drugs these patients were exposed to was 21.3% (1-33.1%) and 2.3 % (0.3-8.2%) respectively. The percentage of cases exposed to different contaminated cases were as follows: Promethazine oral solution BP ML 21 - 202, 16/22 (72.7%), Kofexmaline Baby Cough Syrup ML 21 –

199, 2/22(9.1%), Makoff Baby Cough Syrup ML 21 – 203, 2/22 (9.1%) and MaGrip n Cold Syrup ML 2 – 198, 3/22 (13.6%). One case took two drugs Promethazine ML 21 - 202 and Magrib n Cold Syrup ML 2- 198, 1/22(4.5%).

Table 2: Clinical characteristics of the AKI cases with likely exposure to DEG/EG

Variable	**Likely exposure to DEG/EG: n=22 (100%)**
Age (months)	
Mean	22.9
Median (IQR)	20 (11-27)
Sex	
Male	13 (59.1)
Female	9 (40.9)
Symptoms	
Fever	21 (95.5)
Vomiting	21 (95.5)
Oliguria/anuria	22 (100)
Loose stools	12 (54.6)
Cough	6 (27.3)
Duration of admission: Median (IQR) days	3 (1-5)
	n=16
Urea at admission: Median (IQR) mmol/l	29.8 (16.7-39.9)
Creatinine at admission:(Median (IQR) umol/l	746 (666.7-905.9)
Total short term mortality	22 (100)
Number of cases that took Contaminated medications (%):	
Promethazine oral solution BP ML 21-202	16 (72.7)
Kofexmaline Baby Cough Syrup ML 21-199	2 (9.1)

Makoff Baby Cough Syrup ML 21-203	2 (9.1)
MaGrip n Cold Syrup ML 2-198	3 (13.6)
Combined Promethazine ML 21-202 and Magrib ML 2-198	1 (4.5)

Characteristics of cases with unknown/uncertain exposure to DEG/EG

Thirty-four out of the 56 assessed cases (60.7%) fulfilled the case definition for acute kidney injury (AKI) but had unclear exposure history regarding medicines used (Table 3). Of note, is that the exposure history may be unclear for several reasons (e.g. unclear recall by the parents, lack of toxicologic testing of the administered medicines, failure to declare the dispensing of the concerned batches by pharmacy staff) and does not per Se exclude that the children were exposed to the medicines implicated in the cases with confirmed exposure.

Four (4) of the 34 children had possible alternative / contributing diagnosis (see flowchart) but it is impossible to exclude DEG/EG poisoning as potential cause of AKI with certainty.

The median age of the cases was 18.5 (IQR, 8-25) months, with 24 (70.6%) being males. All cases were admitted to hospitals (suggesting the possibility that cases with AKI may have been missed if not seen at a healthcare facility). The median time from admission to death was 4 (IQR, 2-5) days.

The majority of children presented initially with fever 33/34 (97.1%) vomiting 31/34 (91.2%) and oliguria/anuria 29/34 (89.3%). The Median values of urea and creatinine for these cases at presentation were as follows; 28.5 (IQR 20.4-37.1) mmol/l and 664 (IQR 511-834) µmol/l, respectively. Overall mortality was 100% (see flowchart).

Table 3: Clinical characteristics of the AKI cases with unknown/uncertain exposure to DEG/EG

Variable	**Unknown/uncertain exposure to DEG/EG: n=34 (100%)**
Age (months)	
Mean	22.3
Median (IQR)	18.5 (8-25)
Sex	

Male	24 (70.6)
Female	10 (29.4)
Symptoms	
Fever	33 (97.1)
Vomiting	31 (91.2)
Oliguria/anuria	29 (89.3)
Loose stools	13(38.2)
Cough	13(38.2)
Duration of admission: Median (IQR) days	4 (2-5)
	n=27
Urea at admission: Median (IQR) mmol/l	28.5(20.4-37.1)
	n=26
Creatinine at admission:(Median (IQR) umol/l	664 (511-838)
Total short term mortality	34 (100)

THE SUMMARY OF CAUSALITY ASSESSMENT FINDINGS IN THE GAMBIA 2022

1. # of cases assessed = 69
2. # of cases that meets the case definition = 56
3. # of cases that did not meet the case definition = 3
4. # of cases with insufficient data for in-depth review = 10
5. # of cases assessed as likely exposed to DEG or EG = 22
6. # of cases with suspected poisoning with pending toxicity results or uncertain exposure = 30
7. # of cases with possible alternative/contributing diagnoses identified by CAC = 4

SUMMARY OF AUTOPSIES:

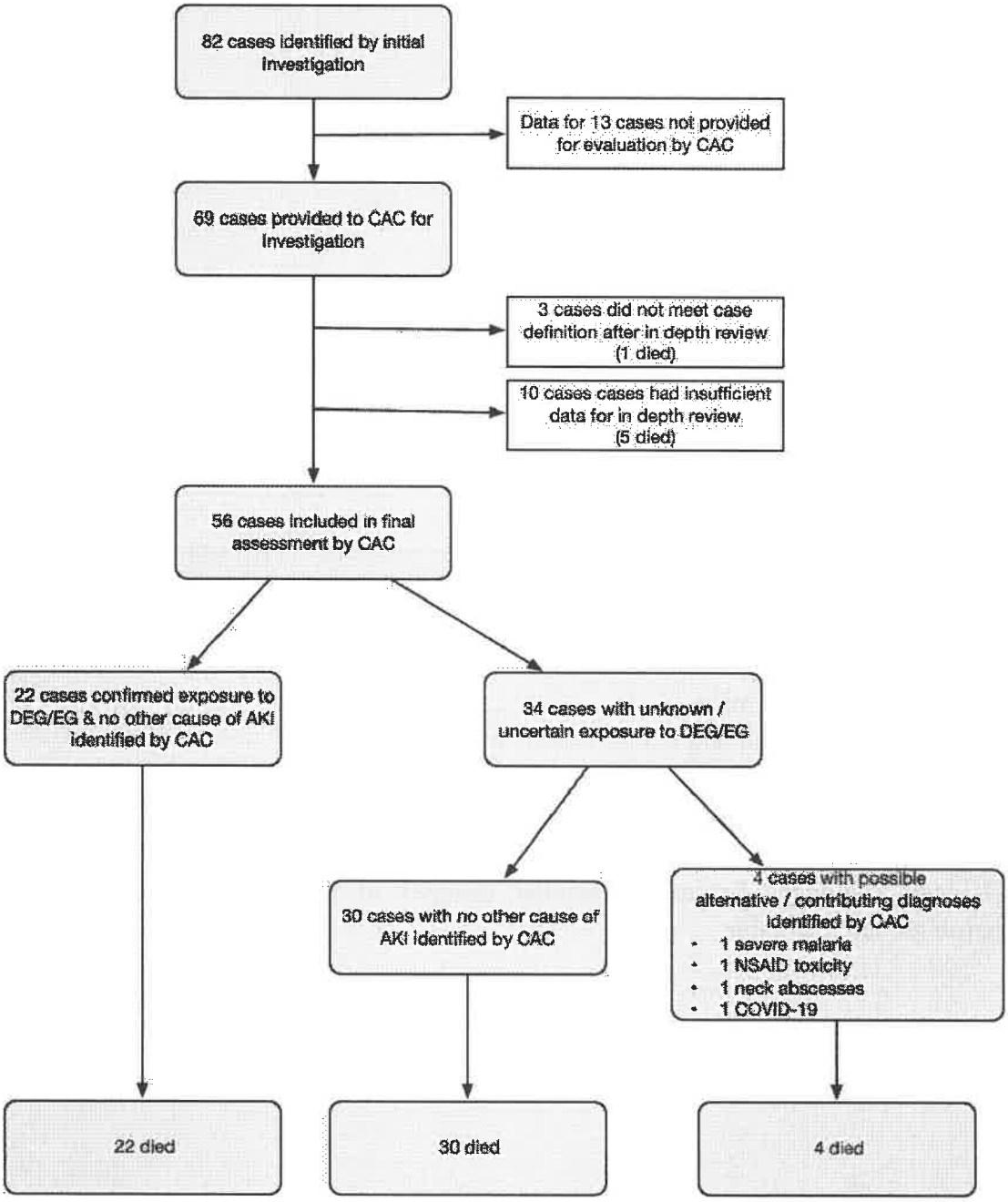
Two of the AKI cases with unknown/uncertain exposure to DEG/EG had autopsy that confirmed renal and hepatic pathological findings consistent with features of DEG/EG poisoning. Below are the summaries of the 2 autopsies that were conducted in the suspected cases. Only these two cases had autopsy in the whole series of deaths

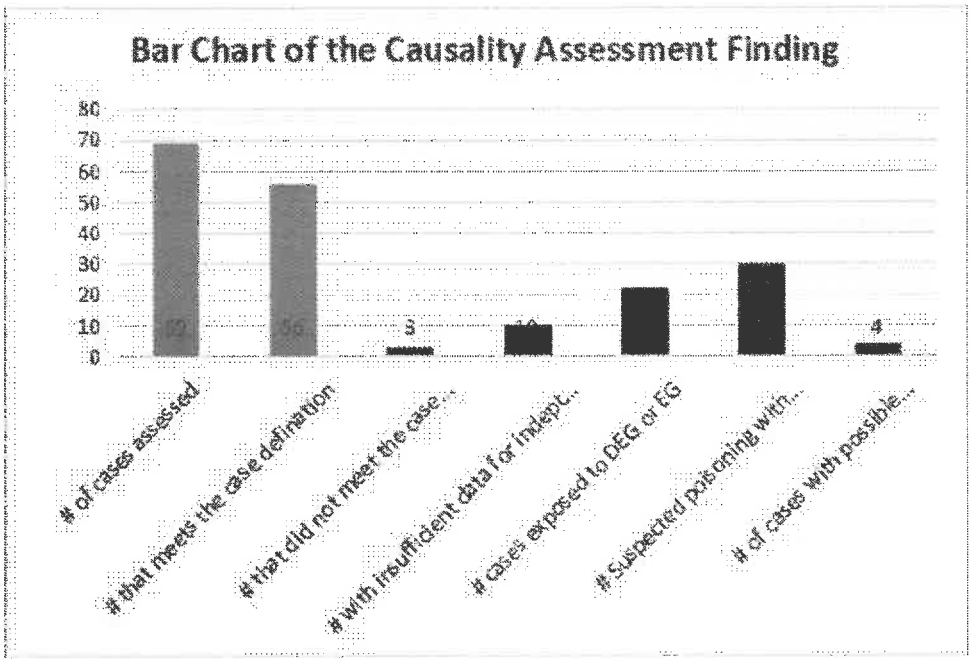
recorded, as follows:

Case 1 summary of autopsy findings:
1. Age: 8 months
2. Sex: Female
3. Under weight (4.2kg), 60% of expected weight
4. Diffuse cortical parlor
5. Fatty liver
6. Splenic congestion
7. Extensive dermatitis
8. Liver histology: Zone 1 & 2 microvesicular steatosis
9. Kidney histology: Extensive vacuolar changes of tubular epithelial cells. Glomeruli are unremarkable.

Case 2 summary of autopsy findings:
1. Age: 11 months
2. Sex: Male
3. Severely underweight (4.8kg), 53% of expected
4. Bilateral cortical parlor
5. Severe fatty liver
6. Mild pulmonary congestion
7. Pedal edema, fluffy hair and reduce muscle bulk
8. Splenic congestion
9. Liver histology: Diffuse macrovesicular steatosis with multifocal hepatic cell necrosis and associated mild periportal fibrosis.
10. Kidney histology: Extensive vacuolar changes of tubular epithelium. The glomeruli are unremarkable.

Flowchart of the Causality Assessment Finding:





SUMMARY STATEMENT OF THE RESULTS

Based on the detailed review of 56 cases of AKI in children in the Gambia DEG/EG poisoning could be confirmed as a cause of AKI and death in 22 children. For the remaining 34, DEG/EG poisoning also needs to be considered as likely cause in at least 30 despite absence of confirmed exposure given the epidemiologic context, the absence of other identified causes, the notorious difficulty to assess medicine exposure in detail and the fact that two children in this group had autopsy findings suggestive of DEG/EG poisoning. In summary, the CAC certify that the outbreak of AKI in children in the Gambia is attributable to medicines contaminated with DEG/EG.

RECOMMENDATIONS OF THE CAC

Strengthening appropriate use of medicines

The contaminated products were mostly obtained over the counter without medical consultation dispensed at pharmacy outlets. The active ingredients of the medicines have no proven benefit for the indications for which they were prescribed. Poly-pharmacy (use of several medicines) was common with several products having the same active ingredients, which is unnecessary, and increases risk of adverse events or even poisoning. Education of the public is particularly important to change parents demand for inappropriate prescribing and dispensing of medicines. There is thus a need to educate the public / parents, and healthcare professionals about the appropriate use of medicines. This could be achieved through public campaigns and educational interventions for health care professionals. Rapid implementation of

educational campaigns while the memory of the outbreak is still fresh would be important.

Training of more pharmacists e.g., through establishment of a pharmacy school (currently only 28 pharmacists in the country) also seems important.

Pharmacovigilance and Toxicovigilance

Pharmacovigilance should be strengthened. Educate healthcare professionals about pharmacovigilance and processes to follow. Strengthen the national pharmacovigilance unit and establish a poison information center to help in preventing, diagnosing and treating acute poisonings, particularly in young children. Data collection during the outbreak investigation could be strengthened by increased use of electronic data capturing tools and implementation of electronic health record.

Strengthening clinical laboratory services

Provision of adequate and standard laboratory facilities are key in the investigating and managing cases of adverse events of any cause. There is a need to provide modern laboratory equipment for clinical evaluations of patients in tandem with current scientific medical evolution.

Registration and quality control of medicines

Care should be taken to enforce regulations and to ensure no unregistered medicines could be imported and dispensed in the Gambia. Assurance of the quality of medicines for use in a country by drug regulatory authorities is the method of choice to prevent outbreaks like the one analyzed in this report. However, in Gambia testing of all batches of medicines seems presently not possible. Establishment of a quality control laboratory for batch testing is timely and important. Collaboration with other countries with stringent regulatory bodies in the region seems advisable for now. The best circumstance would be, in-country means of screening batches of medicines.

CONCLUSION

The world has once again, experienced another epidemic of AKI secondary to DEG & EG poisoning due to substandard pharmaceutical formulations that led to fatal outcomes.

When all the above recommendations are established we anticipate the minimization of these kind of poisoning in licensed medicines and this type of epidemic.

REFERENCES

A Abubukar, E Awosanya,O Badaru,S Haladu, P Nguku. Fatal Poisoning Among Young Children from Diethylene Glycol-Contaminated Acetaminophen --- Nigeria, 2008--2009 MMWR-CDC December 11, 2009/58(48);1345-1347.

Alkahtani, S., Sammons, H., Choonara, I., 2010. Epidemics of acute renal failure in children (diethylene glycol toxicity). Archives of Disease in Childhood 95, 1062–1064.

Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36(3):205-13. doi: 10.3109/15563659809028940. PMID: 9656975.

Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ Jr, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. BMJ. 1995 Jul 8;311(6997):88-91. doi: 10.1136/bmj.311.6997.88. PMID: 7613408; PMCID: PMC2550149.

Landry Greg M., Dunning Cody L., Conrad Taylor, Hitt Mallory J., McMartin Kenneth E., 2013. Diglycolic acid inhibits succinate dehydrogenase activity in human proximal tubule cells leading to mitochondrial dysfunction and cell death, Toxicology Letters 221 (2013) 176–184, https://doi.org/10.1016/j.toxlet.2013.06.231.

Lauren M. Besenhofer, Marie C. McLaren, Brian Latimer, Michael Bartels, Mark J. Filary, Adam W. Perala and Kenneth E. McMartin, 2011. Role of Tissue Metabolite Accumulation in the Renal Toxicity of Diethylene Glycol, Toxicological Science, 123(2), 374–383 doi:10.1093/toxsci/kfr197.

Marraffa, J., Holland, M., Stork, C., Hoy, C., Hodgman, M., 2008. Diethylene glycol: widely used solvent presents serious poisoning potential. Journal of Emergency Medicine 35, 401–406.

O'Brien KL, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr DB, Barr JR, Hospedales CJ, Lewis MJ, Schwartz B, Philen RM, St Victor S, Espindola J, Needham LL, Denerville K. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. Acute Renal Failure Investigation Team. JAMA. 1998 Apr 15;279(15):1175-80. doi: 10.1001/jama.279.15.1175. PMID: 9555756.

Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36(3):205-13

Yannick Arimone, Irene bidault, Jean-paul, et. al. Updating the French Method for the Causality Assessment of Adverse Drug Reactions. Vol 68, Issue 2, March April 2013, https://doi.org/10.2515/therapie/2013016.

ANNEXES

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A. Terms of Reference for Causality Assessment Committee Members for Causality Assessment of Acute Kidney Injury (AKI) in The Gambia

Background

On the 26th July 2022, the Epidemiology and Disease Control Unit received a report through the Director of Health Services from a Nephrologist indicating a sudden increase in the number of cases of Acute Kidney Injury (AKI) among children aged 2 months to 7 years being treated at the Edward Francis Small Teaching Hospital (EFSTH).

AKI refers to an abrupt decrease in kidney function that happens within a few hours or a few days. AKI causes a build-up of waste products in the blood and makes it hard for the kidneys to keep the right balance of fluid in the body. Some of the signs and symptoms of AKI include oliguria or anuria, oedema, confusion, nausea, diarrhoea, shortness of breath, chest pain, coma among others.

A case definition was developed, and active case search revealed additional cases. The index case was traced to 4th July 2022. As of 2 November 2022, about 83 cases of AKI had been confirmed with 70 reported deaths (CFR 85%).

About 72% of the cases were under the age of two years. Cases were reported from six out of the country's seven health regions, with 87% of cases reported from three health regions (Western Region 1 and 2 and Upper River Region).

Clinical features among cases include fever (81% of cases), vomiting (61%), diarrhoea (51%) and cough (10%). The average duration of illness was nine days (range 5 - 18 days). This is the first known outbreak of AKI in the country.

Stool samples test results from 62 children with acute watery diarrhea (AWD) showed 38 (61%) tested positive for E. coli, including two samples positive for Shiga toxin-producing E. coli (O157:H7). In addition, nine samples of medicines (Paracetamol, promethazine, and Cough syrups) taken by children with AKI were sent for toxicological tests, and some of the medications were found to contain diethylene glycol and ethylene glycol.

Autopsy of the 2 deceased cases revealed complete fatty necrosis of their liver and desiccation of their kidney parenchyma.

It is against this background that the Ministry of Health and the Medicines Control Agency is convening a technical expert meeting to undertake the causality assessment on the AKI victims in The Gambia.

Justification

Given that medications have been implicated in the hospitalization and death of these children; It is recommended that a causality assessment be conducted in order to evaluate the relationship between the uptake of the medication and the observed event.

Duties and Responsibilities

The expert/staff will work closely with The Gambia's Ministry of Health (MoH), the Medicines Control Agency (MCA) and the Edidemiology and disease control (EDC) unit to facilitate the implementation causality assessment by performing the following tasks:

- Work with the National Expert Committee on ADR to conduct the causality assessment on for the AKI under the secretariatship of MCA
- With WHO as an observer of the entire process
- In collaboration with the EDC, Edward Francis Small Teaching Hospital (EFSTH) and MCA to request for any valuable document that would guide the ease of the assignment
- To come up with the most plausible causal association that led to the AKI
- To summarize the final points for communication to The Gambians on the cause of the AKI by the Minister of Health

Additionally, the expert/staff should Perform any other duties as assigned by the secretariat.

Deliverables

The following deliverables are expected.

- Situation report submitted to WR and AFRO
- Final mission report

Duty Stations: The Gambia

Contract Duration: Two (2) Weeks
Academic qualifications Essential: University degree in one of the disciplines relevant to the following areas: Social Sciences, Medicine, Health, Public Health

Desirable: Professor in the field of Pathology (morbid anatomy), Toxicology, Clinical Pharmacologist or other related public health fields.

Other Skills: Excellent knowledge on various methods of causality assessments (e.g. Swedish method by Wilholm et al, Danguamou's french method, WHO - Uppsala causality assessment criteria, Naranjo scale, Bayesian adverse reaction diagnostic instrument [BARDI], etc).

Experience

- At least 10 (Ten years) of relevant work experience as an expert in Medicine, Pharmacology or Social sciences
- Proven experience working in multi-stakeholder settings
- A member of national causality assessment committeee is an added advantage
- Experience with WHO or other agencies in the United Nations system would be an asset
- Proven skills in the implementation of public health preventive programs
- Ability to work as a team under tight deadlines and work in a multicultural environment.
- Demonstrated experience of working in collaboration with a wide range of stakeholders.

Working Languages

- Excellent knowledge of English.

Competencies:

- Producing results
- Communicating in a credible and effective way
- Building and promoting partnerships across the organization and beyond
- Respecting and promoting individual and cultural differences.

B. LIST OF CAUSALITY ASSESSMENT COMMITTEE MEMBERS

S.N	Name & E-mail	Specialization	Designation	Institution	Position
1.	Prof. Abdou Niang niangabdou@ucad.edu.sn	Internal Medicine & Nephrology	Consultant	Cheikh Anta Diop University, Dakar. Senegal	**CAC - Chairman**

2.	Prof. Mamadou Fall madoufal@gmail.com	Toxicology	Consultant	Poison Control Center, Dakar. Senegal	Member
3.	Dr Kalle Hoppu kalle.hoppu@fimnet.fi	Paediatrics, Clinical Pharmacology, Clinical Toxicology	Consultant	Helsinki University Hospital, Helsinki. Finland	Member
4.	Dr Benedikt Huttner bhuttner@who.int	Infectious diseases & Essential Medicine	Consultant	WHO Geneva, Switzerland	Member
5.	Dr John N. Jabang jjabang@utg.edu.gm	Neurosurgery	Consultant	Edward Francis Small Teaching Hospital, Banjul. The Gambia	Member
6.	Dr Adegboye Adedotun adedutch2002@yahoo.com	Cardiology	Specialist	Bafrow Medical Center, Serekunda. The Gambia	Member
7.	Dr Sheikh Omar Bittaye sobittaye@utg.edu.gm	Internal Medicine	Specialist	Edward Francis Small Teaching Hospital, Banjul. The Gambia	Member
8.	Dr Abdoulie Badjan badjanj@gmail.com	Microbiology	Specialist	Edward Francis Small Teaching Hospital, Banjul. The	Member

				Gambia	
9.	Dr Ousman Leigh Leighousman80@gmail.com	Pathology	Specialist	Edward Francis Small Teaching Hospital, Banjul. The Gambia	Member
10.	Prof. James Coulson **(virtually)** CoulsonJM@cardiff.ac.uk	Clinical Pharmacology, Toxicology and Internal Medicine		All Wales Toxicology Centre, University Hospital, United Kingdom.	Member
11.	Dr Adamu D. Dawud dr.addawud@gmail.com	Epidemiology	Consultant	WHO The Gambia	**CAC - Secretary**

C. AGENDA FOR THE CAC MEETING

Venue: **Salon Amina Hall** - Senegambia Hotel, Gambia

Date: 05 - 09 December 2022

Time: 9am – 5pm daily

Day 1: Monday 5th December 2022

S/No.	Time allocated	Item	Mode	Responsible person
1.	8:30 – 9:00am	Registration & Admin Announcements	Signing of attendance register	All
2.	9:00 - 9:05am	Opening prayers		All
3.	9:05 – 9:20am	Welcome address	Short speech	Hon. MoH/Perm Sec MoH
4.	9:20 – 9:30am	Opening remarks	Short speech	DHS WCO – WR

5.	9:20 - 9:40am	Overview of the AKI situation in The Gambia	PPT	EDC
6.	9:40 - 10:00am	Brief overview by the Paediatricians	PPT	EFSTH
7.	10:00 – 10:20am	Q & A		All
8.	10:20 – 11:00	Tea Break		All
9.	11:00 – 12:00	Joint Committee of Experts to have a presentation on Method for the AKI CA	PPT	Any of the Core members
10.	12:00 – 1:30pm	Q & A		All
11.	1:30 – 2:45pm	Prayers & Lunch		All
12.	2:45 – 3:45pm	Nomination of the Chairperson by the Committee members		ED MCA
13.	3:45 – 4:00pm	Signing Declaration of Impartiality, No Conflict of Interest and Confidentiality Form		Committee Members only
14.	4:00 – 4:45pm	Assessment evaluations for AKI		Chairperson
15.	4:45 – 4:50pm	Closing remarks		DHS
16.	4:50 - 5:00pm	Closing prayers		All

Day 2: Tuesday 6th December 2022

S/No.	Time allocated	Item	Mode	Responsible person
1.	8:30 – 9:00am	Registration	Signing of attendance register	All
2.	9:00 - 9:05am	Opening prayers		All
3.	9:05 – 9:30am	Assessment evaluations for AKI		Chairperson
4.	9:30 – 10:00am	Tea Break		All

5.	10:00 – 2:30pm	Assessment evaluations for AKI		Chairperson
	2:30 – 3:30pm	Lunch break		All
6.	3:30 – 4:30pm	Assessment evaluations for AKI		Chairperson
7.	4:30 – 4:45pm	Assessment evaluations for AKI		Chairperson
8.	4:45 – 4:55pm	Closing remarks		DED -MCA
9.	4:55 - 5:00pm	Closing prayers		All

Day 3: Wednesday 7th December 2022

S/No.	Time allocated	Item	Mode	Responsible person
1.	8:30 – 9:00am	Registration	Signing of attendance register	All
2.	9:00 - 9:05am	Opening prayers		All
3.	9:05 – 9:30am	Assessment evaluations for AKI		Chairperson
4.	9:30 – 10:00am	Tea Break		All
5.	10:00 – 2:30pm	Assessment evaluations for AKI		Chairperson
6.	2:30 – 3:30pm	Lunch break		All
7.	3:30 – 4:30pm	Assessment evaluations for AKI		Chairperson
8.	4:30 – 4:45pm	Assessment evaluations for AKI		Chairperson
9.	4:45 – 4:55pm	Closing remarks		DED -MCA
10.	4:55 - 5:00pm	Closing prayers		All

Day 4: Thursday 8th December 2022

S/No.	Time allocated	Item	Mode	Responsible person
1.	8:30 – 9:00am	Registration	Signing of attendance register	All
2.	9:00 - 9:05am	Opening prayers		All

3.	9:05 – 11:00am	Assessment evaluations for AKI		Chairperson
4.	11:00 – 12:00pm	Tea Break		All
5.	12:00 – 2:30pm	Assessment evaluations for AKI		Chairperson
6.	2:30 – 3:30pm	Lunch break		All
7.	3:30 – 4:30pm	Summarizing report for AKI CA findings		Chairperson
8.	4:30 – 4:45pm	Draft 1 of the CA for AKI findings		Chairperson
9.	4:45 – 4:55pm	Closing remarks		DED -MCA
10.	4:55 - 5:00pm	Closing prayers		All

Day 5: Friday 9th December 2022

S/No.	Time allocated	Item	Mode	Responsible person
1.	8:30 – 9:00am	Registration	Signing of attendance register	All
2.	9:00 - 9:05am	Opening prayers		All
3.	9:05 – 11:00am	Final CA report for the AKI in The Gambia		Chairperson
4.	11:00 – 12:00pm	Tea Break		All
5.	12:00 – 2:30pm	Communication draft for the Minister of Health		Chairperson
6.	2:30 – 3:30pm	Lunch break		All
7.	3:30 – 4:30pm	Signing of the written report for the AKI CA by members		Chairperson & Members
8.	4:30 – 4:45pm	Submission of signed Report to the ED - MCA		Chairperson
9.	4:45 – 5:00pm	Closing remarks		DED -MCA
10.	5:00 - 5:05pm	Closing prayers		All

MEDICINES CONTROL AGENCY

54 Kairaba Avenue, K.S.M.D. Pipeline, The Gambia Telephone(+220)4380632

Confidentiality Agreement

The person named below will keep confidential any information acquired in the course of the work for or on behalf of the Medicines Control Agency (MCA) and agrees not to disclose such information to any third party at any time without prior written consent of the MCA, save where such information is already in the public domain through no fault of either party, and where either party is required by law to make a disclosure.

Both parties shall undertake all reasonable steps to ensure that any documents or other materials and data or other information which are supplied to the other party and are clearly marked as confidential, remain confidential to the parties. The parties will only make such information available to those who have a reasonable need to know of it and the documents or other materials and data or other information or copies thereof will not be made available to any third parties.

This obligation of confidentiality will remain in force beyond the cessation or other termination of the work for or on behalf of the MCA.

I, ...

hereby agree that all information in relation to the Medicines Control Agency, whether gained by myself prior to, during or after an assignment, will be treated by myself as confidential information and will not be disclosed to any person or organisation, unless authorised to do so.

Signed: ..... Date: .....

Signed: ..... Date: .....

MCA Authorised Representative

CONFLICT OF INTEREST DECLARATION PROCEDURE

This declaration is made through signing of a form by each member of the AKI causality assessment committee. It is sent to the Ministry of Health and released as needed.

Before each committee meeting (plenary session, extraordinary session) this declaration is prepared by the Medicines Control Agency (MCA) as the Secretariat for any adverse drug reaction based on potential changes related to items on the agenda.

The members of the committee who did not complete a conflict-of-interest declaration must withdraw from the committee or its working groups. Any reported interests may be revealed during the meeting, possibly published succinctly online and/ or made available to the public upon request.

MANAGEMENT OF CONFLICT OF INTEREST

Affirmative answers to the questions on the form will not lead to the *de facto* exclusion or limitation of participation in committee meetings of the member involved. The committee Chairman is responsible for the analysis of the completed forms to determine the potential existence of a conflict of interest.

After examining the contents of the conflict-of-interest declaration form, the Chairman

may decide whether or not a conflict of interest applies and whether this is a minor or major implicssation.

If the Chairman reports a conflict of interest, the secretariat applies one or a combination of the following three options:

A. The member may be invited to attend meetings or work on condition that his/her interest is publicly disclosed.
B. The member may be asked not to take part in a portion of the meeting, discussions or work in relation to his/her interest or not to participate in related decision-making.
C. The member may be asked not to take part in the meeting or work portion of the meeting.

THE USUAL PROCEDURE IS AS FOLLOWS:

- Members with a specific personal interest will be asked to leave the room for the discussion and decision-making.
- Members with a non-specific personal interest may participate in discussions but may not take part in the decision-making.
- Members with specific non-personal interests may answer direct questions from the Chair but may not take part in the decision-making.
- Members with non-specific non-personal interest may take part in the discussions and the decision-making.

Any conflict of interest is publicly disclosed to other participants at the beginning of activities and in the report or any other document produced at the end.

In an audit or further examination, the contents of a member's conflict of interest declaration form could be made available to persons who are not part of the AKI committee if the member's objectivity is disputed, and the Chairman of the committee considers revelation as a major concern for their credibility.

By completing the attached form the member hereby agrees to these terms.

CONFLICT OF INTEREST DECLARATION FORM

(To be filled by each member of the Acute Kidney Injury (AKI) causality assessment committee in The Gambia)

Title, First names & Last name: .....

Professional Designation: .....

1. Are there factors that can affect your impartiality in the work relating to the items on the agenda?

Yes

No

If so, explain:

2. Could the findings of this work positively or negatively affect the interests of persons

with whom you are personally or professionally related (child over the age of majority,

siblings, colleagues, etc.)?

Yes

No

If so, explain:

3. Do you have any financial interest (shares, bonds, or equity instruments) in the company producing or marketing the product under review or of the direct competitor?

Yes

No

4. Have you been owner, manager, partner, employee, member of a decision-making body of the company producing or marketing the product under review or of the direct competitor in the last three (3) years?

Yes

No

5. Have you been involved in any other types of regular activities for the company producing or marketing the product under review or for the direct competitor in the last three (3) years?

Yes

No

6. Have you been involved in any scientific work (tests, studies, evaluation etc.) with the company producing or marketing the product under review or with the direct competitor in the last three (3) years?

Yes

No

If so, what kind?

Epidemiological studies related to the disease under study

Clinical trials

Other (specify):

Did you receive financial remuneration?

Yes

No

7. Have you attended a meeting (conference, symposium, training, etc.) organized by the company producing or marketing the product under review or by the direct competitor in the past three (3) years?

Yes

No

If so, in what context?

- Speaker
- Participant
- Member of the organizing/scientific committee
- Other (specify)

Travel and accommodation expenses covered by the company

Yes

No

Fees paid by the company

Yes

No

Other (specify):

8. Have you received financial support from a partner (organization, institution, foundation etc.) in the past three (3) years for conducting an activity that might have a link with any activity on the agenda?

Yes

No

9. Are any of your relatives employed by the company producing or marketing the product under review or as the direct competitor?

Yes

No

If yes,

· Spouse

· Child

· Other (specify):

Comments:

I declare on my word of honour that the information provided above is true and complete. I also undertake to inform the Secretariat of AKI Committee (MCA) The Gambia of any subsequent changes and complete a new form to describe any applicable changes.

Date:

Signature:

EDC
EPIDEMIOLOGY & DISEASE CONTROL

World Health Organization

Standard Case Definitions for Acute Kidney Injuries (AKI)

Community/Alert Case for AKI: A child 8 years old or younger with any of the following symptoms: fever, vomiting, diarrhea, cough, with or without reduced urine output.

Suspected Cases: A child 8 years old or younger with any of the following symptoms: fever, vomiting, diarrhea, cough, with history of syrup consumption.

OR

A child 8 years old or younger with any of the following symptoms: fever, vomiting, diarrhea, cough with reduced urine

OR

A child 8 years old or younger with reduced urine output

Probable Case:

Any suspected case who died without confirmation

Confirmed Cases:

Any suspected case with acute onset of either oliguria or anuria of unknown etiology* lasting for more than 24 hours.

OR

A suspected case confirmed with serum creatinine level that indicates renal failure

Collaborators: MoH (EDC, NPHL, MCA), WHO, MRC, AFENET, US CDC, RTSL, UNICEF, MoWR, PURA, GRCS

*We exclude the common causes such as dehydration, malaria, and others.

MEDICINES CONTROL AGENCY, THE GAMBIA

Medicines Control Agency
54 Kairaba Avenue
TEL: (+220) 9946188 /4380632/3515273

Reporting Form for Suspected Adverse Drug Reactions *(STRICTLY CONFIDENTIAL)*

1. *PATIENT'S DETAILS

Full Name or Initials: _____ Patient Record No: _____
AGE/DATE OF BIRTH: _____ SEX: M ☐ F ☐ WEIGHT (Kg): _____
HOSPITAL/ Treatment Center: _____

2. *ADVERSE DRUG REACTION (ADR)/ADVERSE EVENT

A. DESCRIPTION

DATE Reaction Started	DATE Reaction Stopped

C. OUTCOME OF REACTION
TICK AS APPROPRIATE
☐ Recovered fully ☐ Recovered with disability ☐ (Specify) _____
☐ Congenital Abnormality (Specify) ☐ Life Threatening (Specify) _____
Death ☐ Others (Specify) ☐

B. Was Patient Admitted Due to ADR Yes ☐ No ☐

If Already Hospitalized, Was It Prolonged Due to ADR Yes ☐ No ☐

Duration of Admission (days) _____
Treatment of Reacton: _____

3. *SUSPECTED DRUG(including Biologicals, Traditional/Herbal medicines)

A. DRUG DETAILS(state name and other details if available/ attach product label/ Sample (available)
Brand Name: _____ Generic Name: _____ Batch No. _____
MCA No: _____ Expiry Date: _____
Name & Address of Manufacturer: _____

B.

Indication for use	Dosage	Route of Administration	Date Started	Date Stopped

4. *CONCOMITANT MEDICINES(All medicines taken within the last 3 months including herbal and self medication)

Brand or Generic Name	Dosage	Route	Date started	Date stopped	Reason for use

5. *SOURCE OF REPORT:

Name of Reporter: _____
Address: _____
Profession: _____
Signature: _____ Date: _____ Tel No/E-mail:

H. SUMMARY OF THE MEDICINES ANALYSIS RESULTS FROM MCA

The Nine (9) Medicines sent to Ghana's first batch for testing are the same nine medicines sent to France and the 23 Medicines sent to Switzerland also included the Nine (9) Medicines sent to Ghana's first batch and France for confirmatory.

38 Medicines sent to Ghana, France and Switzerland for analysis,

34 has passed the test with no Ethylene glycol and Diethylene glycol present.

4 products from Maiden Pharmaceuticals were found to contain both Ethylene glycol and Diethylene glycol.

1. Promethazine oral solution BP
2. Kofexmalin Baby Cough Syrup (Pheniramine Maleate, Ammoium chloride, Menthol)
3. MaKOFF BABY Cough Syrup(Chlorphenamine Maleate, Phenylephrine HBR , Dextromethophan syrup)
4. MaGrip n Cold Syrup (Paracetamol BP 125mg,Phenylephrine HCL BP 2.50mg, Chlorphenamine Maleate BP 1mg)

All 34 products found not to contain EG and DEG were released for marketing on 11th November, 2022

CONTAMINATED MEDICATIONS LABORATORY ANALYSIS DATA FROM THE DIFFERENT LABORATORIES

Contaminated medications	**United States Pharmacopeia laboratory Ghana (%)**	**Centre Humanitaire Des Metiers De La Pharmacie (CHM) France (g/l)**	**Itertek (Schweitz) AG, Switzerland (%)**
Promethazine oral solution BP ML 21-202	Ethylene Glycol= Constituting about 22% Diethylene Glycol= Constituting about 11%	Ethylene Glycol= 32.53g/L Diethylene Glycol=500.08g/L	Ethylene Glycol=2.3% Diethylene Glycol=21.3%
Kofexmaline Baby Cough Syrup ML 21-199	Sample was not sent	Sample was not sent	Ethylene Glycol=2.0% Diethylene Glycol=2.3%
Makoff Baby Cough Syrup ML 21-203	Sample was not sent	Sample was not sent	Ethylene Glycol=0.3% Diethylene Glycol=1.0%
MaGrip n Cold Syrup ML2-198	Sample was not sent	Sample was not sent	Ethylene Glycol=5.9% Diethylene Glycol=11.8%

I. Summary of The French Method of Causality Assessment for ADR

The French method of imputability causality assessment scale was used to determine the causal relationship between the DEG & EG in the syrups ingested by the children for a reasonable possibility of any toxicity that might have led to the Acute Kidney Injury (AKI).

This method consists of both intrinsic (effects of DEG & EG) and extrinsic (available literatures) accountability. The imputability considers three components; the chronological (C), the Semiological (S) and the imputability (I) that indicates the causal relationship. The C and S scores were assessed with the information reported and together they determine the intrinsic imputability (I).

The extrinsic (B) imputability is assessed by using the current literature available.

PICTURES DURING THE CAUSALITY ASSESSMENT MEETING

Group work during the CA evaluation process