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Original article

Retrospective application of brief resolved unexplained event (BRUE) criteria on infants admitted with ALTE or suspected sepsis: a 5-year analysis in a single tertiary center in Western Saudi Arabia

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Abstract

Background: In 2016, the American Academy of Pediatrics (AAP) proposed a criteria definition and management guidelines for brief resolved unexplained events (BRUE) in replacement of the apparent life-threatening events (ALTE). In this study, we report the findings of a retrospective application of BRUE criteria. We estimated the prevalence of BRUE among neonates and infant's emergency visits and analyzed and discussed the clinical presentations and management patterns.

Methods: We reviewed the medical charts of 1,212 infants aged less than 1 year who were admitted to the Pediatric Medical Emergency Ward (PMEW) at a tertiary care hospital in Western Saudi Arabia from January 2011 to January 2016. Infants who were discharged with ALTE or without a final diagnosis were assessed regarding the AAP BRUE. Demographic, clinical, and follow-up data were collected and analyzed.

Results: Nineteen infants (12 females, age range = 4-90 days) were retrospectively classified as BRUE, representing 1.6% (95%CI = 1.0-2.4%) of the overall neonates and infants' visits at the PMEW; 13 of them were initially classified as ALTE; at the same time, the 6 remainders were suspected of sepsis. The most frequently reported symptom was cyanosis (14, 73.7%), followed by absent breathing (11, 57.9%) and altered consciousness (4, 21.1%). Notably, 14 (73.7%) patients had at least 2 concomitant symptoms. The majority (17, 89.5%) met the high-risk criteria. Sixteen out of the 19 benefitted from further investigations and were hospitalized, with a median length of stay of 3 days.

Conclusion: BRUE accounted for 1.6% of the overall neonates and infant emergency visits in our institution, and one-third of them were initially classified other than ALTE. The application of 2016 AAP BRUE guidelines

is highly recommended as it offers a practical management strategy for infants who experience non-evident symptoms, guided by a comprehensive assessment of the risk level related to the patient's history and living environment, regardless of the initial symptom.

Keywords

Apparent life-threatening event, brief resolved unexplained events, suspected sepsis, prevalence, prognosis, Saudi Arabia.

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Introduction

Brief resolved unexplained events (BRUE) represent a recent clinical classification incorporating an array of sudden, brief, and spontaneously resolutive symptoms occurring in infants aged less than 1 year having no etiological explanation. The first clinical practice guidelines issued by the American Academy of Pediatrics (AAP) suggested the "BRUE" designation in replacement of the apparent life-threatening events (ALTE) and proposed a criteria definition and risk evaluation of such events. According to the AAP, BRUE symptoms should include at least 1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness. The diagnosis is established by the exclusion of any underlying condition that may explain the event, after a meticulous analysis of the infant's history and an appropriately led physical examination. Thus, the presence of any additional symptom or abnormal sign should rule out the diagnosis of BRUE and lead to further investigation [1-3].

BRUE constitutes a perplexing clinical dilemma that confronts a frightening experience, reported as a near-death event, with an asymptomatic and well-appearing child. For many physicians, the absence of clinical signs on examination impedes the choice of appropriate work-up or makes it unjustified. In some cases, work-ups may be carried out based on the clinician's intuition or to relieve the pressure of concerned or dissatisfied parents, for whom an absence of diagnosis may be highly frustrating [4, 5].

Therefore, the AAP guidelines provided a practical algorithm for risk classification and management of BRUE, besides the previously presented diagnostic criteria. Risk stratification applies 5 criteria for low-risk levels, including age > 60 days, gestational age 32 weeks or older and postconceptional age ≥ 45 weeks, absence of cardiopulmonary resuscitation (CPR) by a trained medical provider, an event lasting less than 1 minute, absence of a similar event in history, and no concerning historical features or physical examination findings. Any infant not meeting 1 of these criteria is considered a high-risk patient [1, 2]. Based on this classification, infants who meet low-risk BRUE criteria are discharged after a brief observation in the Emergency Ward and reassurance and education of caregivers. Conversely, those classified as high-risk should be hospitalized to further evaluate common causes of apneic events such as respiratory infection, gastroesophageal reflux disease (GERD), or trauma [4].

Data regarding BRUE is insufficient to address an accurate epidemiological picture due to its recent classification and inconsistent presentation. Previously, ALTE was reported among 0.6% to 0.8% of infants visiting the Emergency Ward, accounting for 2.5 to 4.1 hospital admissions per 1,000 live births [6-8]. Some authors attempted to establish a correlation between ALTE and BRUE by retrospectively applying the AAP criteria on pre-existing data and found that only 23% to 58% of ALTE cases can be reclassified as BRUE [9-11]. Consequently, BRUE appears to be distinct, yet it is an ill-defined entity that may encompass various clinical presentations and have variable prognostic significance.

In this study, we reported the findings of a retrospective application of BRUE criteria over 5-year data preceding the publication of the AAP guidelines. Thereby, we estimated the prevalence of BRUE among neonates and infants' emergency visits in a tertiary care center, analyzed and discussed the clinical presentations and management patterns.

A retrospective chart review was conducted in the Pediatric Medical Emergency Ward (PMEW) at King Abdulaziz University Hospital, Jeddah,

Saudi Arabia, from January 2011 to January 2016, which corresponds to the 5 years preceding the publication of the BRUE guidelines. We reviewed the medical records of all infants aged less than 1 year who were admitted to the PMEW with different diagnoses and clinical presentations, such as neonatal sepsis, bronchiolitis, neonatal jaundice, suspected sepsis, etc., as well as those who were classified as ALTE. Those who were discharged with a definitive diagnosis were excluded, while those discharged with no final diagnosis were assessed for the criteria of BRUE. The study protocol was approved by the institutional review board of King Abdulaziz University (reference number 140-19), Jeddah, Saudi Arabia.

BRUE definition was applied according to the AAP guidelines, including sudden, brief, yet resolved episodes of cyanosis or pallor, abnormal breathing, marked change in tone, and altered level of responsiveness. Other criteria included the absence of clinical explanation in the patient's history, and physical examination [1]. All infants who did not meet these criteria were excluded.

Further, the level of risk was assessed, and infants were classified as low-risk if they met the following criteria: age older than 60 days; gestational age 32 weeks or older and postconceptional age ≥ 45 weeks; no previous BRUE ever; event lasting < 1 minute; no CPR required by a trained medical provider; and no concerning historical features or physical examination findings. Failure to meet at least 1 of these criteria was considered high risk [1].

Demographic and clinical data such as age, gender, clinical presentation, investigations, management, and follow-up were collected.

Statistical methods

Statistical analysis was performed with the Statistical Package for Social Sciences® version 21.0 for Windows® (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean ± standard deviation (SD).

Results

BRUE cases' definition

A total of 1,212 infants were admitted to the PMEW during the study period. Of these, 227 infants were presented with suspicion of sepsis, while 985 infants were presented with other complaints. Six (2.6%) out of 227 infants admitted for suspicion of sepsis had been ruled out; all met the BRUE criteria. Of the 985 who had a miscellaneous presentation, 13 (1.3%) had been initially classified as ALTE; all 13 fulfilled the BRUE criteria.

Thus, 19 infants were retrospectively classified as BRUE, representing 1.6% (95%CI = 1.0-2.4%) of the overall neonates and infants' visits at the PMEW (**Fig. 1**).

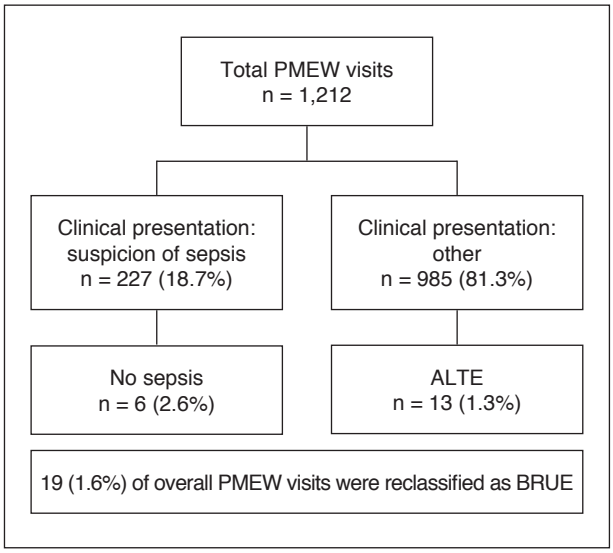

Figure 1. Flowchart of retrospectively diagnosed BRUE cases.
ALTE: apparent life-threatening events; BRUE: brief resolved unexplained events; PMEW: Pediatric Medical Emergency Ward.

Demographic and clinical characteristics of BRUE patients

There were 12 females among the 19 BRUE patients (female:male ratio = 1.7). Age ranged between 4 and 90 days, with a mean (SD) = 30.9 (19.6) days. The majority were born from term pregnancy (14, 73.7%), and only 2 had a significant, unrelated history, including a Pediatric Intensive Care Unit (PICU) admission for apnea and a Neonatal Intensive Care Unit (NICU) admission with 2-week continuous positive airway pressure (CPAP) therapy. Sixteen out of the 19 were hospitalized, with a median length of stay of 3 days and a maximum of 10 days. Additionally, 16 benefitted from further investigations, and 12 received antibiotic therapy, as shown in **Tab. 1**.

Table 1. Patients' characteristics.

Parameter	Category	Frequency [b]	Percentage [b]
Initial presentation/classification	ALTE	13	68.4
	Suspicion of sepsis	6	31.6
Gender	Male	7	36.8
	Female	12	63.2
Age (days)	Mean, SD	30.9, 19.6	
	Median, interquartile	30.0, 21.0	
	Range	4-90	
Gestational age	Term	14	73.7
	Preterm	5	26.3
Significant history	No	17	89.5
	Yes [a]	2	10.5
Management mode	Admission	16	84.2
	ER observation	3	15.8
Hospital stay (days)	Mean, SD	3.4, 2.7	
	Median, interquartile	3.0, 4.0	
	Range	0-10	
Investigated	No	3	15.8
	Yes	16	84.2
Antibiotic therapy	No	7	36.8
	Yes	12	63.2
Follow-up	Unremarkable	18	94.7
	Abnormality (inguinal hernia)	1	5.3

ALTE: apparent life-threatening event; ER: Emergency Room; SD: standard deviation.
[a] Case 1: history of Pediatric Intensive Care Unit (PICU) admission for apnea and suspected sepsis; case 2: twin pregnancy admitted to Neonate Intensive Care Unit (NICU) with 2-week continuous positive airway pressure (CPAP) therapy.
[b] Data are presented as frequency and percentage if not otherwise indicated.

Clinical manifestations and risk level for patients identified as BRUE

The most frequent clinical manifestation was cyanosis (14, 73.7%), followed by the absence of breathing (11, 57.9%) and altered consciousness (4, 21.1%). Notably, 14 (73.7%) patients had at least 2 concomitant symptoms, as demonstrated in **Tab. 2**. Assessment of risk level showed the majority being classified as high-risk (17, 89.5%); all 17 were aged < 60 days, and 5 of them were premature as described in **Tab. 3**. Notably, 2 out of the 17 infants who were classified as high-risk had not been hospitalized nor they benefitted from paraclinical investigations.

Lab and imaging investigations

Tab. 4 presents all hematology, enzymology, biochemistry, microbiology, and radiological investigations that were carried, with the respective number and percentage of participants who benefitted from the given investigation, number and percentage of abnormal results, and summary of the results as mean (SD) for numerical

Table 2. Clinical manifestations for patients identified as BRUE.

Criteria/symptoms		Frequency	Percentage
Cyanosis or pallor		16	84.2
Cyanosis		14	73.7
Pallor		2	10.5
Abnormal breathing		14	73.7
Absent breathing		11	57.9
Decreased breathing		1	5.3
Irregular breathing		2	10.5
Change in tone		2	10.5
Hypotonia		2	10.5
Hypertonia		0	0.0
Altered level of consciousness		4	21.1
Number of concomitant symptoms	1	5	26.3
	2	11	57.9
	3	3	15.8
Symptom features	Sudden	19	100.0
	Brief	19	100.0
	Resolved	19	100.0

BRUE: brief resolved unexplained events.

Table 3. BRUE risk stratification.

Criterion	Met (low risk)		Unmet (high risk)	
	Frequency	Percentage	Frequency	Percentage
Age > 60 days	2	10.5	17	89.5
Born ≥ 32 weeks and postconceptional age ≥ 45 weeks	14	73.7	5	26.3
No CPR by trained medical staff	17	89.5	2	10.5
Event lasted < 1 minute	19	100.0	0	0.0
First event [a]	19	100.0	0	0.0
Overall	2	10.5	17	89.5

BRUE: brief resolved unexplained events; CPR: cardiopulmonary resuscitation.
[a] No previous BRUE ever, and no concerning historical features or physical examination findings.

Table 4. Lab and imaging investigations.

Investigation		Done		Results				
				Abnormal		Mean	SD	Unit
		Frequency	Percentage	Frequency	Percentage			
Hematology	**White blood cell count**	16	84.2	0	0.0	10.75	3.03	K/µL
	Hemoglobin	16	84.2	6	31.6	13.38	2.78	g/dL
	Platelets	16	84.2	8	42.1	431.25	93.38	K/µL
	Neutrophils	14	73.7	1	5.3	2.87	2.20	K/µL
	Lymphocytes	14	73.7	2	10.5	6.04	2.27	K/µL
Proteins and enzymes	**Albumin**	11	57.9	0	0.0	31.91	2.55	g/L
	ALT	7	36.8	0	0.0	25.00	9.59	U/L
	AST	7	36.8	0	0.0	39.14	17.16	U/L
	GGT	7	36.8	0	0.0	171.00	135.67	U/L
	SB	7	36.8	0	0.0	115.57	74.57	µmol/L
	DB	5	26.3	0	0.0	6.60	2.61	µmol/L
	ALP	9	47.4	0	0.0	293.11	115.50	U/L
Biochemistry	**Glycemia**	6	31.6	0	0.0	4.92	1.49	mmol/L
	Sodium	16	84.2	3	15.8	137.06	2.02	mmol/L
	Potassium	16	84.2	7	36.8	5.11	0.45	mmol/L
	Urea	16	84.2	0	0.0	2.74	1.52	mmol/L
	Creatinine	16	84.2	0	0.0	27.00	14.56	µmol/L
	Calcium	9	47.4	0	0.0	2.42	0.14	mmol/L
	Magnesium	6	31.6	0	0.0	0.89	0.13	mmol/L
	Phosphate	9	47.4	0	0.0	2.05	0.29	mmol/L
	CRP	15	78.9	0	0.0	-	-	-
Microbiology	**Blood culture**	15	78.9	0	0.0	-	-	-
	Lumbar puncture	7	36.8	0	0.0	-	-	-
	CSF protein			0	0.0	0.94	0.38	g/L
	CSF glucose			0	0.0	4.86	5.36	mmol/L
	CSF cells count			0	0.0	7.21	7.05	cells/mm^3
	CSF culture			0	0.0	-	-	-
	Urine culture	12	63.2	0	0.0	-	-	-
Radiology [a]		13	68.4	0	0.0	-	-	-

ALP: alkaline phosphatase; ALT: alanine amino transferase; AST: aspartate amino transferase; CRP: C-reactive protein; CSF: cerebrospinal fluid; DB: direct bilirubin; GGT: gamma glutamyl transferase; SB: serum bilirubin; SD: standard deviation.
[a] Radiology included chest X-ray (11, 57.9% patients), Gastrografin® meal (1 patients), barium meal (1 patient) and brain ultrasound (1 patient).

variables. Complete blood count (CBC) was carried out among 16 (84.2%) infants, showing mild anemia among 6 (31.6%) infants, moderate thrombocytosis among 8 (42.1%). Similarly, electrolytes measurement and renal function were carried out among 16 (84.2%) infants showing moderate hypernatremia and hyperkalemia in 3 (15.8%) and 7 (36.8%) patients, respectively. Microbiologically, blood, cerebrospinal fluid, and urine cultures were carried out in 15 (78.9%), 7 (36.8%), and 12 (63.2%) patients, respectively, showing no microbial growth.

Discussion

Summary of findings

This retrospective application of the AAP guidelines showed that BRUE account for 1.6% (95%CI = 1.0-2.4%) of the overall neonates and infant emergency visits, as applied over the 5 years preceding the publication of the guidelines. All infants who had previously been classified as ALTE were reclassified as BRUE. Besides, 2.6% of patients who presented with symptoms evocative of sepsis met the BRUE criteria and were added to the cohort. The majority of these cases were hospitalized and investigated. Interestingly, while approximately 90% of the cases met the high-risk criteria, 2 of them were not hospitalized and were discharged without further investigation. For note, our population is marked by young age, as the oldest participant was 3 months old.

Not all ALTE are BRUE, and not all BRUE are ALTE

Findings from the present study demonstrated that BRUE classification could not be entirely considered as a replacement for ALTE, as suggested by the AAP guidelines [1]. Although all infants initially classified as ALTE met the BRUE criteria, 6 other infants managed as suspected non-confirmed sepsis met the high-risk BRUE criteria. This is inconsistent with findings from other reported retrospective applications of BRUE. For example, Colombo et al. reported 58% of BRUE validated cases among 84 infants initially admitted for an ALTE [11], Ramgopal et al. reported 43% among 762 [10], whereas Meyer et al. reported only 23% among 321 [9]. Such observations support the fact that the new BRUE classification is distinct from the previously used ALTE, and the confusing use of 2 terminologies should be banned from the academic literature. This discrepancy between BRUE and ALTE may be explained by the criteria definition of BRUE, including a specific set of symptoms, and the exclusion of BRUE if a similar episode is reported or in case of suspect history. This level of specificity constitutes the core justification of the AAP recommendations, which aim at alleviating a puzzling clinical presentation by providing clear management guidelines to secure the patient and deal with the panic of both caregivers and health care providers.

All the 6 infants initially diagnosed as suspected sepsis in the present study were hospitalized and investigated, and 5 out of them had a probabilistic antibiotic therapy with no clinical or microbiological evidence of infection. Nontheless, those infants did indeed require a high index of suspicion and careful assessment as they were categorized in the high-risk group, and no recommendations have been offered for this category in the AAP BRUE guidelines. This supports the relevance of promoting the implementation of BRUE guidelines among pediatric emergency physicians to avoid overdiagnosis and overtreatment. Further, besides improving the quality of care by alleviating safety concerns related to mismanagement, the application of BRUE was demonstrated to have a beneficial impact on the health economy by decreasing unnecessary health expenditures by up to 20%. These include lab and imaging work-ups, excessive hospital admissions and long stays, and medications [11-13].

Pathological significance of BRUE

The significance of BRUE as a diagnosis stands in its favorable prognosis, which enables leveling the alertness while providing a clear management approach. Therefore, several authors explored the morbidity and mortality associated with BRUE to provide accurate insight into its pathological significance. A meta-analysis of mortality associated with BRUE showed 0.4% deaths between 6 months and 3 years following the index episode, with an adjusted mortality rate estimated as 3.1 deaths per month per 10,000 BRUE. These rates were considered comparable to the general population [14]. Another retrospective report investigating the long-term prognosis of BRUE showed no significant increase in mortality or the incidence of neurological or cardiovascular morbidity or psycho-developmental delay among children with a history

of BRUE compared with the general population. On the other hand, a higher prevalence of autism spectrum disorders was reported, along with relatively frequent rehospitalizations, notably for recurrent choking events secondary to GERD [15]. Another systematic review reported GERD as the most frequent condition diagnosed among children re-evaluated for ALTE, among a variety of other pathologies such as seizure and lower respiratory tract infection [8]. This is consistent with 1 case from the present study, a 30-day-old male diagnosed with GERD with inguinal hernia 3 months following the BRUE episode. The patient was initially admitted for resolved pallor and absence of breathing and was hospitalized for 3 days. Besides moderate thrombocytosis, work-up showed normal CBC, C-reactive protein (CRP), alkaline phosphatase (ALP), sodium and potassium levels, and renal function. No radiological examination was done, and the patient received antibiotic therapy, including ampicillin + gentamycin. No other cases of morbidity were reported during the follow-up of the other 18 cases.

The association between ALTE and GERD is classically reported in the literature, yet no causal relationship was established. A systematic review, including 18 studies, analyzed extra-esophageal symptoms of GERD and found a high prevalence of respiratory diseases and general respiratory symptoms [16]. We can hypothesize that the high prevalence of respiratory symptoms among infants with GERD may increase the probability of occurrence of BRUE. The same systematic review estimated 20% of the prevalence of ALTE in GERD patients and reported a higher prevalence of GERD and reflux index among children with ALTE. However, such associations were not consistent throughout the studies included in the review [16]. This association was remarkably addressed by Jilani et al., who stressed the difference between gastro-esophageal reflux (GER) and GERD and confronted studies that evidenced their association with BRUE and ALTE with those that evidenced no relationship. Further, the authors highlighted the subjectivity of the BRUE, in that it relies on the caregiver's appreciation of the life-threatening feature of symptoms, while some uncommon breathing patterns may be physiological in infants and neonates [17]. Such remarks suggest that BRUE may be the only manifestation of a single episode of physiological GER, and on the other hand, associations reported of BRUE with GERD may be purely incidental in some cases. This emphasizes the importance of maintaining an objective and clinically-based approach in the assessment and management of the patient and that the application of BRUE guidelines should not interfere with the etiological diagnostic approach.

In this line, Duncan et al. conducted an interesting study, where they demonstrated that the application of the AAP BRUE guidelines did not impact the practice in GER diagnosis and management, including hospital admission rates, frequency of specific diagnostic testing, number of GER diagnoses, cost of care, and frequency of repeat visits among BRUE infants [18]. Moreover, BRUE may be the manifestation of various functional conditions. An example is a reported case of a newborn infant who suffered from a severe BRUE that was found to be associated with a neonatal abstinence syndrome due to selective serotonin uptake inhibitors [19]. Therefore, the optimal attitude towards BRUE is to consider it a symptom and not as a diagnosis, which may or not have a pathological significance.

The other etiological dimension of BRUE that should be explored is the social dimension, which may unveil severe conditions such as child abuse, which was diagnosed in up to 11% of children with BRUE. This sensitive diagnosis can only be made via an appropriate interview by an experienced professional and can be guided by a family history of ALTE and sudden infant death syndrome or by evocative signs such as retinal hemorrhage [20-22]. This dimension should be systematically explored, and emergency physicians should be educated and trained to screen and manage such conditions.

Limitations of retrospective application of BRUE criteria

The retrospective application of the AAP BRUE criteria in the present study and other published studies is limited by frequent data missing, which may impede the generalizability of the results. The retrospective study design is commonly associated with recall bias. Besides, routinely collected data by emergency physicians are not structured to fit the comprehensive items of BRUE, as recommended by the AAP. For example, the social dimension may often be omitted or not adequately investigated. Additionally, data regarding risk level assessment may not be specified in records, such as the duration of BRUE, as well as follow-up data. Consequently, adequate application of BRUE criteria should be made prospectively, using structured, com-

prehensive questionnaires to provide quality data both for clinical and research use.

Conclusion

BRUE accounted for 1.6% of the overall neonates and infant emergency visits in our institution in the 5 years before the implementation of the AAP guidelines, and one-third of them had been managed as suspected infections. The application of 2016 AAP BRUE guidelines is highly recommended as it offers a practical management strategy for infants who experience non-evident symptoms, guided by a comprehensive assessment of the risk level related to the patient's history and living environment, regardless of the initial symptom. This new classification is distinct from the previously used ALTE, and the confusing use of 2 terminologies should be banned from the academic literature. Further prospective, long-term evaluations of AAP guidelines are warranted to establish their clinical utility, safety, and cost-effectiveness and to provide valuable data regarding the epidemiological picture and pathological significance of BRUE.

Take-home messages

- The AAP BRUE definition and risk assessment offer a practical approach for the proper management of frightening, non-evident symptoms reported by parents and caregivers while alleviating the resulting anxiety.
- Not all ALTE are BRUE, and not all BRUE are ALTE.
- BRUE should be considered as a symptom that may have various pathological or physiological significances.
- Healthcare professionals should be educated and trained to explore the social dimension of infants presenting with BRUE and be able to recognize the significant signs and diagnose eventual underlying abnormalities such as child abuse.
- Adequate application of BRUE guidelines would enable improving the quality of care and reduce health expenditure.

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Declaration of interest

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