Q3: Can febrile seizures (simple or complex) be managed at first or second level care by non-specialist health care providers in low and middle income country settings? What is the role of diagnostic tests in the management of febrile seizures by non-specialists in low and middle income settings? For prophylaxis to prevent recurrence of simple or complex febrile seizures, which of the pharmacological interventions when compared with placebo/comparator produce benefit/harm in specified outcomes?

- continuous anticonvulsant therapy
- intermittent anticonvulsant therapy
- intermittent antipyretic treatment

Q3a): Can febrile seizures (simple or complex) be managed at first or second level care by non-specialist health care providers in low and middle income country settings? What is the role of diagnostic tests in the management of febrile seizures by non-specialists in low and middle income settings?

Background

Febrile seizures (FS) are common, with a life time prevalence of 2-6%. The definition of FS is controversial. The International League Against Epilepsy (ILAE) defines FS as “an epileptic seizure occurring in childhood associated with fever, but without evidence of intracranial infection or defined cause. Seizures with fever in children who have experienced a previous non-febrile seizure are excluded (ILAE, 1993). British Paediatric Association suggested "an epileptic seizure occurring in a child aged from six months to five years, precipitated by fever arising from infection outside the nervous system in a child who is otherwise neurologically normal” (Joint Working Group of the Research Unit of the Royal College of Physicians and British Paediatric Association, 1991). Although it is important to distinguish "seizures with fever" and "febrile seizures" in terms of management and prognosis, this is often not possible in many primary health facilities in resource poor countries (Joint Working Group of the Research Unit of the Royal College of Physicians and British Paediatric Association, 1991). Seizures with fever include any seizure in a child of any age with fever of any cause.

For the purposes of this review, the following definitions are used:

- First Level Care – the first level contact with people taking action to improve health in a community. This includes General Practioners, nurses, paramedics, clinical officers, medical officers attending the patient outside the hospital, such as at home, peripheral clinics or outpatient facilities.

• Second Level Care – refers to hospitals, at a community or district level, providing 24 hour access and staffed by doctors and nurses with expertise in resuscitation.

Professional organizations of Italy, United Kingdom and United States of America have provided guidelines for various aspects of diagnosis and management of febrile seizures (Summarized in Table 1). The equipment, drugs and diagnostic tests that should be available for the management of febrile seizures in each of these levels are summarized in Table 2. However, these elements are not available in many health care facilities in resource poor countries. For example, in a survey of first level care facilities in three countries in Africa, only 74% had a benzodiazepine available (Simoes et al, 2003).

Table 1: Recommendations by Professional Organizations on Management of Febrile Seizures

	American Academy of Paediatrics (AAP, 1996)	Joint Working Group of the Research Unit of the Royal College of Physicians and British Paediatric Association, 1991	Italian League Against Epilepsy (Capovilla et al, 2009)
Admission to hospital	Not stated	1. A child aged less than 18 months 2. A complex seizure, i.e, one lasting longer than 20 minutes, with focal features, repeated in the same episode of illness or with incomplete recovery after one hour 3. Early review by a doctor at home not possible 4. Home circumstances inadequate, or more than usual parental anxiety, or parents' inability to	1. A child aged less than 18 months 2. Complex FS 3. FS in children without a reliable familiar context

		cope	
Investigations	In a healthy child with a first simple febrile seizure: 1. A lumbar puncture (LP) should be a) strongly considered in a child younger than 12 months; b) should be considered in children between 12 and 18 months; c) performed in children older than 18 months, on the clinical suspicion of meningitis. 2. Blood tests are not required 3. Electroencephalography (EEG) is not required 4. Neuroimaging is not required	1. Simple FS – none 2. A LP should be performed if: • Clinical signs of meningism; • after a complex convulsion; • child is unduly drowsy or irritable or systemically ill; • if the child is aged less than 18 months (probably) and almost certainly if the child is aged less than 12 months.	1. Simple febrile Seizures in a child > 18 months – None 2. Simple FS in a child < 18 months – consider LP 3. Complex FS a. Blood chemistry b. EEG c. Neuroimaging d. LP
Management	Not stated		1. Remove airway obstruction 2. Prepare a venous access. 3. Monitor vital parameters (heart rate, breath frequency, blood pressure, SaO2). 4. Administer oxygen, if necessary (SaO2

			<90%)
Drugs to stop seizures	Not stated	Not stated	If seizure last> 3min 1. Diazepam 0.5 mg/kg IV 2. Can repeat after 10 mins if seizure not stopped
Prophylaxis against recurrences	Not stated	Not recommended, although occasionally drug prophylaxis may be used for a child who has frequent recurrences.	1. If Simple FS – none 2. Consider prophylaxis in a. Recurrent FS with reliable parents b. > 3 FS in 6 months c. > 4 FS in 1 yr
Education	Not stated	1. An explanation of the nature of FS, including information about the prevalence and prognosis 2. Instructions about the management of fever, the management of a seizure, and the use of rectal diazepam (see above) 3. Reassurance.	1. Describe details of FS 2. Instructions for fever control 3. Discuss prophylactic drugs 4. Education on how to manage possible recurrences: a. Remain calm, no panic; b. Loosen the child's clothing, especially around the neck; c. If the child is unconscious, place the child

			in the lateral decubitus position, to avoid inhalation of saliva or vomitus; d. Do not force opening of the mouth; e. Observe the type and duration of the seizure; f. Do not give any drugs or fluids orally; g. Administer rectal diazepam 0.5 mg/kg, in case of prolonged seizure lasting over 2–3 min. h. In any event, contact the family paediatrician, or other practitioner; i. A medical intervention is necessary in the following cases: • Seizures of a duration >10 min or not remitting after treatment • Recurrent seizures, • Focal seizures, • Presence of prolonged consciousness disorder, and/or postictal palsy

Table 2: Equipment and Supplies for the Diagnosis and Management of Febrile Seizures

		Resource Rich Countries		Resource Poor countries	
		First Level	Second level	First Level	Second level
Equipment	Syringes	✔	✔	✔	✔
	Needles	✔	✔	✔	✔
	Weighing scales	✔	✔	✔	✔
	Refrigerator	✔	✔	(✔)	✔
	Thermometer	✔	✔	✔	✔
Oxygen	Oxygen cylinder	✔	✔	(✔)	
	Oxygen concentrator		✔		
Diagnostic facilities	Blood slide		✔	✔	✔
	Full blood count		✔		✔
	Blood glucose		✔		✔
	Electrolytes		(✔)		(✔)
	Blood culture		✔		(✔)
	Urine Microscopy		✔		✔
			✔		(✔)

	and culture CSF Microscopy and culture CT scan MRI scan		✔ ✔ ✔ (✔) (✔)		✔ (✔) X X
Drugs	Benzodiazepines Phenytoin Phenobarbital	✔ ✔ ✔	✔ ✔ ✔	✔	✔ (✔)

The parents' attitudes to febrile seizures vary considerably around the world. This may effect the presentation and management of FS at primary and secondary care facilities. In an Indian city 59% of parents did not recognize a convulsion and 91% did not perform any interventions before attending hospital (Parmar et al, 2001), whilst in Turkey some parents administered rectal Diazepam (Yilmaz et al, 2008). Provision of leaflets with written instruction to British parents did not appear to significantly improve their knowledge or reduce anxiety about FS (Paul et al, 2007).

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	Children with febrile seizures
Interventions:	Diagnostic tests such as lumbar puncture, blood tests (for malaria parasite, counts, culture), EEG and neuroimaging
Comparison:	Not applicable
Outcomes:	Appropriate diagnosis and improved management

Search strategy

The search strategy was conducted with the search terms outlined in Table 3.

Table 3: Search Strategy for the Management of Febrile Seizures in First and Secondary Level facilities

Breakdown of search remit provided: **Main question:** Can (1) **febrile seizure (2) be managed** at **(3) first** and **(4) second level care?** **Additional variation of terms for Boolean search:** ((febrile seizures) OR (febrile convulsions)) AND ((first level) OR (primary healthcare) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary care))			
Database	**Boolean Search**	**Limits**	**Total**
Pubmed	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient care management)) AND ((first level care) OR (primary healthcare) OR (primary health care) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary level health care) or (secondary care))	Humans, from unspecified and until 2009/01/3. Please note, search was based on partial Boolean: ((febrile seizures) OR (febrile convulsions))	Complete Boolean = 3 Partial Boolean = 2875
Cochrane	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient care management)) AND ((first level care) OR (primary healthcare) OR (primary health care) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary level health	Unable to specify limits	45

	care) or (secondary care))		
PsychInfo		No results even for 'febrile seizures' or 'febrile convulsions'	0
Medline Plus	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient care management)) AND ((first level care) OR (primary healthcare) OR (primary health care) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary level health care) or (secondary care))	Unable to specify limits	1
WHO Africa Index Medicus		Unable to specify limits. No results even for 'febrile seizures' or 'febrile convulsions'	0
WHO Eastern Mediterranean		Unable to specify limits. Database used was EMRO / IMEMR to avoid defaulting to Virtual Health Library or using sub-database, EMCAT. Unable to perform Boolean search ((febrile seizures) OR (febrile convulsions))	'febrile seizures' = 71 'febrile convulsions' = 31
WHO Europe	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient	Unable to specify limits	5

	care management)) AND ((first level care) OR (primary healthcare) OR (primary health care) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary level health care) or (secondary care))		
WHO Latin American & Caribbean	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient care management))	Unable to specify limits. Database search defaulted to Virtual Health Library. Had to specify LILACS. Boolean provided no results beyond this point	5
WHO South East Asia	((febrile seizures) OR (febrile convulsions)) AND ((managed) OR (management) OR (case management) OR (risk management) OR (patient care management)) AND ((first level care) OR (primary healthcare) OR (primary health care) OR (primary care)) AND ((secondary level care) OR (secondary healthcare) OR (secondary level health care) or (secondary care))	Unable to specify limits	21
WHO Western Pacific		Unable to specify limits. Boolean provided only 6 results for ((febrile seizures) AND (febrile convulsions)). There were no results for (febrile convulsions)	(febrile seizures) = 67
Articles chosen out of all database searches			**Total**

performed			
Pubmed			282
			Total accessed
Pubmed			230

INCLUSION AND EXCLUSION CRITERIA

Studies describing the diagnosis and management of children with febrile seizures were reviewed, and some studies that reported children presenting to third level care only were included if they provided information that was helpful to the management of FS in first and second level care.

Studies describing only non-febrile seizures and epilepsy were excluded.

Narrative description of the studies that went into the analysis

The search of the literature did not reveal any randomized control trials of interventions that specifically examined the management of febrile seizures in the primary or secondary care settings

Diagnosis of Febrile seizures

Febrile seizure is syndrome based upon clinical history and observation, and should be differentiated from rigours, febrile delirium, febrile syncope or breath holding attacks. There are no features detected by physical exam that confirm the diagnosis, although examination may detect features of an underlying cause of FS e.g. upper respiratory tract infection or identify other syndromes that cause seizures e.g. neurofibromatosis. Febrile seizures can be caused by a variety of infections, and the diagnostic procedures are aimed at identifying the underlying causes and excluding serious intracranial infections such as acute bacterial meningitis or viral encephalitis that require specific interventions. It is estimated that acute bacterial meningitis occurs in 2-7% of children who present with seizures associated with fever (Fetveit, 2008). Most of this data was gathered before the introduction of vaccines against the main causes of bacterial meningitis and is derived from resource rich countries.

Febrile seizures are defined as simple if they are tonic-clonic, self-limiting, of short duration (<15 minutes), without postictal pathology, and do not recur within the next 24 hours. Febrile seizures are defined as complex if they have longer duration (>15 minutes), or have focal features, or if they recur within 24 hours (multiple seizures). There may be considerable disagreement about the identification of these features, even amongst experts such as paediatric neurologists (Berg et al, 1992).

Blood tests

Blood tests that would be taken for a febrile or ill child e.g. full blood count should be performed according to the local recommendations e.g. blood slide for malaria in endemic areas. Most authorities recommend that blood glucose need not be routinely measured in all children with a febrile seizure (AAP, 1996; Chamberlain and Gorman, 1988; Gerber and Berliner, 1981; Rutter and Smales, 1977). One study of British children presenting with a first febrile seizure found that only 1/269 had hypoglycaemia, although 22 (8%) had hyperglycaemia (Rutter and Smales, 1977). The yield from blood cultures in children with FS is not significantly different to those in febrile seizures presenting to paediatric emergency departments (AAP, 1996; Chamberlain and Gorman, 1988).

Lumbar Puncture

Lumbar punctures (LP) are performed to detect causes of febrile seizures, particularly bacterial meningitis and viral encephalitis. The recommendations for lumbar puncture in the investigation of FS vary with history of previous FS, age (mainly because of the difficulty in detecting bacterial meningitis in young children) and also the prevalence of the common causes of FS in the area.

In a study of 241 children presenting with fever and seizures to an American emergency room, five risk factors predicted meningitis: contact with a doctor 48 hours before the seizure; convulsions on arrival to the emergency room; a focal seizure; suspicious findings on physical and/or neurologic examination (not specified) (Joffe et al, 1983). In a decision analysis the sensitivity of any of a combination of at least two of these factors was 1.0, the specificity was 0.62 and had a negative predictive value of 1.0 for bacterial meningitis. In a study of 328 children presenting to a tertiary hospital with their first febrile seizure, only one child had bacterial meningitis, another had mumps detected and two others had presumed viral infections (Rutter and Smales, 1977).

In 1996, the American Academy of Paediatrics recommended that a LP should be performed in children less than 18 months presenting with their first FS (AAP, 1996). These guidelines were more likely to be followed in community hospitals than tertiary hospitals (Hampers et al, 2000), but in either situation they are rarely followed, such that only 8.4% of children less than 18 months had a LP for investigation of FS in 42 community hospitals in the USA (Hampers et al, 2006). There was a decrease in the adherence to the guidelines over a 10 year period in one American paediatric emergency department, although no

cases of bacterial meningitis were detected (Kimia et al, 2009). Likewise in a recent study, only 28/56 infants with febrile seizures had a LP in a tertiary hospital, and none had bacterial meningitis (Shaked et al, 2009).

In resource poor countries, where the incidence of serious central nervous system infections is high, lumbar punctures may be indicated in children presenting with fever and seizures. A study of 111 children presenting with febrile seizures to a tertiary hospital in Iran, identified 4 children with bacterial meningitis although 3 had other signs of meningitis (Shiva and Hashemian, 1998). In a study of Ghanaian children presenting to a tertiary hospital with fever and seizures, where 186/608 admitted had LP done, 19 (10.2%) had bacterial meningitis (Owusu-Ofori et al, 2004).

One of the issues of LP in RPC is that in many countries, the health care staff that work in first level care facilities are not allowed to perform LP (Simoes et al, 2003), and there is inadequate laboratory training or facilities to process the specimens.

In complex febrile seizures the yield from LP is low. In one study of 315 children primarily (i.e. not referred) presenting to a Canadian tertiary centre with complex febrile seizures, one child had bacterial meningitis and this was associated with lethargy (Seltz et al, 2009).

Electroencephalography

Electroencephalography (EEG) can detect abnormalities of the brain cortex, including epileptic discharges. It is used to classify seizures, but is not necessary for the confirmation of the seizure disorders. It has been suggested as useful for predicting seizures and the occurrence of epilepsy.

EEG is not recommended in children with simple or complex FS. The prevalence of paroxysmal EEG abnormalities in children with FS varies widely from 2 to 86% (Maytal et al, 2000). The reasons for this wide variation include differences in ages and the selection of patients for EEG, the aetiology of the FS, differences in the definition of paroxysmal discharges, the period between the occurrence of the FS and the EEG.

The EEG adds little to the diagnosis in simple FS (Gerber and Berliner, 1981; Maytal et al, 2000). It is not useful in predicting recurrence of seizures either FS or epilepsy (Kuturec et al, 1997; Stores, 1991).

In a study of 33 children with complex FS who did not have any neurological abnormalities, all the EEG were normal (Maytal et al, 2000). In a retrospective study of 175 children who had EEG following complex FS, 39% had abnormalities (slow waves, focal and/or generalized abnormalities of the background rhythm and/or the presence of interictal epileptiform activity (sharp waves, spikes, and/or spike wave complexes) detected on the EEG (Joshi et al, 2005). The independent predictive factors of abnormal EEGs were; age >3 years, EEGs performed within 7 days and an abnormal neurological exam, whilst a family history of febrile seizures was associated with a normal EEG (Joshi et al, 2005). However in Turkey, 45% of children with complex FS assessed at a tertiary centre had abnormalities on their EEGs, although the EEGs did not appear to change management (Stores, 1991; Yucel et al, 2004).

Neuroimaging

The skull and brain can be imaged with a skull X-ray, computerized tomography (CT) and magnetic resonance imaging (MRI). CT and MRI facilities are often not available in secondary care facilities, particularly in resource-poor settings. There is no evidence that skull x-ray are useful in the diagnosis of FS. CT scans abnormalities were found in 3/17 children who presented with complicated febrile seizures to an emergency department at a tertiary hospital (Garvey et al, 1998), whilst in another American study none of the 13 patients with complex FS had abnormal CT scans. MRI is more sensitive than CT scan. A study of 159 children presenting their first FS, detected abnormalities on 20 (13%) MRI scans, with increased prevalence in those with focal seizures, but these findings did not change the management of the child, unless there were other neurological features (Hesdorffer et al, 2008). In 17 Japanese children with prolonged FS, transient abnormalities were seen on diffusion weighted imaging and T2-weighted images between 9-13 days after the seizure (Natsume et al, 2007; Takanashi et al, 2006). However CT scans or MRI did not detect any intracranial pathology that required emergency treatment in 23 children presenting with complex FS to a tertiary hospital (Teng et al, 2006).

In Turkey, cranial CT detected abnormalities 5/36 children with complex FS and 5/9 who had postictal neurological deficits (Teng et al, 2006; Yucel et al, 2004). However it did not detect any abnormalities in the 27 children with focal seizures.

a) Risk of meningitis in children presenting with febrile seizures.

There are several hospital studies of variable validity looking at the probability of meningitis. The signs that were found to indicate an increased risk of meningitis in a child with seizure and fever were: drowsy pre-seizure, neck stiffness, petechial rash, bulging fontanelle, a Glasgow Coma Scale of <15 (more than one hour post seizure) (Offringa et al, 1992b; Offringa and Moyer, 2001). This was rated as Level III evidence and Delphi consensus, grade C recommendation.

b) Management of the child with febrile seizure and no focus of infection

No published evidence was found to address this issue. The need for a good urine sample collected without contamination was agreed in the first round of a Delphi consultation carried out by the authors of the systematic review. The recommendation was that a child who has had a simple febrile seizure, where no source for infection has been found clinically, should have a urine sample (clean catch, SPA or catheter specimen) taken for microscopy and culture. On the second round two statements with equal weight were proposed, i.e., children with no focus for infection can be admitted for a short period of observation (minimum two hours) or can be discharged home if the child looks well, as long as the parents/carers have ready access to health care and they are happy with this decision. This was based on the Delphi consensus only, since there was no published evidence.

c) Complex febrile seizures

The literature suggests that complex febrile convulsions (defined above) are predictive of CNS infection (Green et al, 1993; Joffe et al, 1983; Offringa et al, 1992a; Offringa and Moyer, 2001). The risk of bacterial meningitis in children presenting with fever and seizure is about 3% (McIntyre et al, 1990) and with a complex seizure is about 9%.

After the first Delphi round it was agreed that children with complex seizures should be admitted to hospital. After admission it was recommended that a child presenting with a complex febrile seizure (defined above) with no clinical signs of meningitis should be observed closely and reviewed within two hours by a paediatrician of at least Registrar/Resident level to decide on need for LP.

Referral from First level care

Seizures are one of the danger signs that the World Health Organization's Integrated Management of Childhood Illness (IMCI) suggests that the child should be referred to a second level facility (WHO, 2005). In one study of 151 children aged 2 months to 5 years who presented with convulsions to first level care facilities in three countries in Africa, it was suggested that only 12% needed to referred to a second level facility, since they had other signs such as lethargy, impaired consciousness and/or unable to drink (Simoes et al, 2003). There have been no other studies that have addressed this question within this setting.

Education

Explanation and education about FS of the parents and/or guardians is an important component of the management of FS at all levels. This includes explanation about the causes of FS, the diagnostic procedures that may be performed to exclude serious infections and the outcome of the FS. Further advice about preventing recurrence and initiating treatment may be helpful in appropriate circumstances.

Methodological limitations

Most of the studies did not clearly state the facilities available for the diagnosis and management of FS in their reports.

Directness (in terms of population, outcome, interventions and comparison)

Most of the studies identified had been conducted in tertiary emergency departments, and none comprehensively examined the diagnosis and management of FS in first or second level care. There were no audits of the management of FS in primary care settings.

Narrative Conclusion

No published studies were identified that specifically addressed the question as to whether FS could be managed at first level care or secondary level care. However the studies that examined the components of the management of FS (particularly the drug management) at these facilities and consensus statements from Western experts were identified, suggest that simple FS (particularly if it is the first FS) may be managed a first level facilities, although those children with features of complex FS may need to be referred to second level care. Investigations rarely influence management, except that the exclusion of central nervous system infections is important, particularly in children less than 18 months old.

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Q3b) In febrile seizures, which of the pharmacological interventions when compared with placebo/comparator produce benefit/harm in specified outcomes?

- Continuous anticonvulsant therapy

- Intermittent anticonvulsant therapy

- Intermittent antipyretic treatment

Background

Febrile seizures (FS) are common, with a life time prevalence of 2-6%. The definition of FS is controversial. The International League Against Epilepsy (ILAE) defines FS as “an epileptic seizure occurring in childhood after 1 month of age associated with fever, but without evidence of intracranial infection or defined cause. Seizures with fever in children who have experienced a previous non febrile seizure are excluded” (ILAE ,1993). The Joint Working Group of the Research unit of the Royal College of Physicians and the British Paediatric Association suggested "an epileptic seizure occurring in a child aged from six months to five years, precipitated by fever arising from infection outside the nervous system in a child who is otherwise neurologically normal (Joint Working Group of the Research Unit of the Royal College of Physicians and British Paediatric Association, 1991)." The Consensus in Medicine (1980) definition of a febrile seizure is "an event in infancy or childhood usually occurring between 3 months and 5 years of age associated with a fever, but without evidence of intracranial infection or defined cause for their seizure", after having excluded children with previous febrile seizures. For the purpose of this profile, we follow the lower age limit of 6 months, given concerns regarding the possibility of an underlying serious but treatable infection in younger infants masquerading as a febrile seizure (e.g. meningitis).

Although it is important to distinguish "seizures with fever" and "febrile seizures" in terms of management and prognosis, this is often not possible in many primary health facilities in Low and Middle Income Countries (LMIC). Seizures with fever include any seizure in a child of any age with fever of any cause.

Febrile seizures are defined as simple if they are generalized, often tonic-clonic, self-limiting, of short duration (<15 minutes), without postictal pathology, and do not recur within the next 24 hours. Febrile seizures are defined as complex if they have longer duration (>15 minutes), or have focal features, or if they recur within 24 hours (multiple seizures). In developed countries, simple febrile seizures predominate but in developing countries, fever-associated seizures are often complex febrile seizures. The literature suggests that complex febrile convulsions are predictive of CNS infection (Joffe et al, 1983; Offringa et al, 1992; Offringa and Moyer, 2001; Green et al, 1993). In Australia, the risk of bacterial meningitis in children presenting with fever and seizure is about 3% (McIntyre et al, 1990) and with a complex seizure is about 9%. In Kenya, a study found 84% of children with malarial fevers and seizures had

complex seizures with 47% being focal and over 70% repetitive (Waruiru et al, 1996). There may be considerable disagreement about the identification of these features, even amongst experts such as paediatric neurologists (Berg et al, 1992).

About 2–5% of children in the USA and Western Europe, and 6–9% of infants and children in Japan will have experienced at least one febrile seizure, simple or complex, by the age of 5 years. Elsewhere the incidence varies, being 5–10% in India, and as high as 14% in Guam. There are no specific data available for simple febrile seizures. (Mewasingh, 2008)

For simple febrile seizures, prophylactic therapy is advocated by some because of the concerns that such seizures lead to additional febrile seizures, to epilepsy, and perhaps even to brain injury. Moreover, they note the potential for such seizures to cause parental anxiety. The recognition for favourable outcomes with the treatment needs to be balanced with the risk of any treatment and potential adverse effects. The therapeutic approaches that have been considered include intermittent antipyretic therapy, intermittent anticonvulsant therapy and continuous anticonvulsant therapy.

Febrile seizures should be classified as complex when a child presents with a prolonged seizure even though it is stopped with an anticonvulsive therapy before the 15th minute. Complex febrile seizures (CFS) indicate entities with variable etiology, semiology, and prognosis. Therefore, treatment depends upon the etiologic and nosographic picture (Capovilla et al, 2009). A CFS may result from an acute disorder of the CNS or could be simply a prolonged febrile seizure. Admission is recommended for observation because of the wide variability of conditions underlying this event. Search for underlying etiology is recommended in case of CFS. The risk of bacterial meningitis in children presenting with fever and seizure is about 3% and in a complex seizure about 9% (Armon et al, 2003). Children with following features - at least 3 days of illness, seen by GP in previous 24 hours, drowsiness at home, vomiting at home, CFS, petechaie, suspected nuchal rigidity, bulging fontanelle, and focal neurological signs - have an increased risk of meningitis.

The vast majority of children who present with febrile seizures do not develop epilepsy. However, complex febrile seizures are associated with an increased risk of epilepsy. There are other risks factors for epilepsy, including neurological abnormality, family history of epilepsy, and short duration of fever (<1hr) before the seizure. Children without any risks factors have a 2.4% chance of developing a febrile seizure by 25 yrs compared with 1.4% for the general population. Children with a history of at least 1 complex feature, a neurological abnormality, and a family history have a 10% risk of developing epilepsy by the age of 7. Prolonged febrile seizures increase the incidence of epilepsy to 21%. For children with all 3 features of a complex febrile seizure, the risk increases to 49% (Sadleir et al, 2007).

In CFS, prophylactic therapy might be advocated because of concerns of aggravation and epilepsy. However, favourable outcomes need to be balanced with the risks associated to anticonvulsant therapy. Prophylactic treatment is considered in case of recurrent prolonged febrile seizures (Capovilla et al, 2009).

Addressing parental anxiety forms a key part of the management of simple febrile seizures, as parents' (unspoken) worry with a first seizure is that their child might have died. However, there is little in the medical literature about this aspect of education and reassurance in management of simple febrile seizures.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	children with febrile seizures
Interventions:	intermittent antipyretic treatment (paracetamol, ibuprofen, physical methods)
	intermittent anticonvulsant treatment (intermittent diazepam)
	continuous anticonvulsant treatment (phenobarbital, valproate)
Comparison:	no treatment
Outcomes:	prevention of recurrence of febrile seizure
	epilepsy
	adverse effects of drugs

List of the systematic reviews identified by the search process

SEARCH STRATEGY: Cochrane database, NICE guidelines, SIGN guidelines, BMJ clinical evidence, PUBMED search for reviews, clinical queries (term "simple febrile seizure")

INCLUDED IN GRADE TABLES OR FOOTNOTES

The systematic reviews and RCTs included in the PICO table are based on the Clinical Evidence (Mewasingh, 2008).

PICO table (one row for each GRADE table)

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews identified	Systematic review/evidence used for GRADE and explanation
Intermittent antipyretic treatment				
1	**Physical methods of temperature reduction vs. antipyretic drugs/placebo**		No systematic review or RCT identified;	
2	**Antipyretic drugs vs. placebo**	Prevention of recurrence of febrile seizures *Adverse effects*	El-Radhi & Barry, 2003 Meremikwu, *2007*	*Meremikwu, 2007, Analysis 1.2, comparison 1*
Intermittent anticonvulsants				
3	**Intermittent diazepam vs. placebo or no treatment**	Prevention of recurrence of febrile seizures *Adverse effects* Risk of subsequent epilepsy	Masuko et al, 2003; Temkin, 2001; Pavlidou et al; 2006 *Not reported in the above two reviews but data provided by some of the included studies; Pavlidou et al, 2006* No systematic review; Knudsen et al, 1996 (RCT)	Review by Masuko et al is more recent, the two reviews identified three of the RCTs, searched and included Portuguese and Spanish studies, although one RCT is reported differently in two reviews* To provide the narrative information (not GRADEd) Single study (Knudsen et al, 1996)
4	**Intermittent clobazam vs. placebo or no treatment**	Prevention of recurrence of febrile seizures	No systematic review, 2 RCTs reported in BMJ clinical evidence (Mewasingh 2008)	Rose et al, 2005; Bajaj et al, 2005

		Adverse effects	*Same as above*	
5	**Intermittent vs. continuous anticonvulsant**		No systematic review or RCT identified	
Continuous anticonvulsants				
6	**Continuous Phenobarbital vs. placebo or no treatment**	Prevention of recurrence of febrile seizures *Adverse effects* Risk of subsequent epilepsy	Masuko et al, 2003; Temkin, 2001 *Not reported in above two reviews but data provided by some of the included studies; Camfield et al, 1979* No systematic review; Wolf & Forsythe, 1989 (RCT)	Temkin 2001 - 8 RCTs (all 6 that are included in Masuko 2003), both reviews found heterogeneity among trials.
7	**Continuous valproate vs. placebo or no treatment**	Prevention of recurrence of febrile seizures *Adverse effects* Risk of subsequent epilepsy	Temkin, 2001 *Not reported in the above review* No systematic review or RCT	
8	**Continuous Phenobarbital vs. continuous valproate**	Prevention of recurrence of febrile seizures *Adverse effects*	Masuko et al, 2003 No information from the review or included RCT	One RCT from the systematic review (Mamelle et al, 1984)

		Risk of subsequent epilepsy	No information from the review or included RCT	

Narrative description of the studies that went into the analysis (including a study-by-study table if appropriate):

Intermittent diazepam vs. placebo or no treatment:

*****Masuko, 2003 and Temkin, 2001 **-** Study by Knudsen et al, 1985 included in the review by Temkin 2001 was excluded by Masuko 2003 because although the authors describe the study as randomized, the description according to the systematic reviewers presented contrary evidence. Masuko et al, 2003 also searched for articles in Portuguese and Spanish and included Mosquera, 1987, which is not included in Temkin, 2001. In Masuko et al, 2003, the recurrence rates for this RCT are reported as 7/202 (3.5%) in children taking diazepam and 29/204 (14.2%) in children taking placebo; in Temkin, 2001, they are reported as 37/202 (18.3%) in children taking diazepam compared with 53/204 (30%) in children taking placebo. These may explain how reviews with predominantly the same included RCTs came to different conclusions. The mode, dose, and frequency of administration of diazepam varied in each RCT. Most of the RCTs identified by the reviews had weak methods. The first RCT was small. In the second RCT, 50 children (25%) taking diazepam and 55 children (27%) taking placebo were lost to follow-up. The third RCT reported poor compliance in children taking diazepam, which was significantly different from those taking placebo.

Pavlidou et al, 2006: In a prospective randomized cohort trial, 139 children who experienced a first febrile seizure were allocated to two groups: group A, which received intermittent diazepam (n=68), and group B, which received no prophylaxis (n=71). All children had a 3-year follow-up. The inclusion criteria were no personal history of afebrile seizures, normal neurodevelopment, no previous anticonvulsant therapy, and age between 6 months and 3 years. Children with complex febrile seizures (approximately 19%) and febrile status epilepticus (approximately 3%) were also included. Each group was stratified to low, intermediate, and high risk according to the available clinical data. The 36-month recurrence rates in the no-prophylaxis group were 83% in high-risk patients, 55% in intermediate-risk patients, and 46% in low-risk patients. In the prophylaxis group, the recurrence rates were reduced in all risk groups: 38%, 35%, and 33%, respectively. Intermittent diazepam at times of fever reduced the recurrence risk significantly in high-risk children (P=0.005, significant), whereas in low-risk (P=0.412, not significant) and intermediate- risk (P=0.341, not significant) patients, it had limited efficacy.

Adverse effects - The study reported that adverse effects with diazepam were mild and transient, and no long-term side effects were recorded during the 3-year follow-up (no further numerical data or statistical analysis of adverse effects between groups reported).

Knudsen et al, 1985: In a prospective randomized study, 289 children admitted consecutively to hospital with their first febrile seizure were allocated, by date of admission, to short term diazepam prophylaxis (n=152) or to no prophylaxis (n=137) and followed for 18 months. In untreated children, five major risk factors for recurrent febrile convulsions were identified: age 15 months or less at the time of the first febrile seizure, epilepsy in first degree relatives, febrile convulsions in first degree relatives, a first complex febrile seizure, and day nursery care. The 18 month recurrence rate was 80 to 100% if three to five risk factors were present, 50% if two factors were identified, 25% where one factor was found, and 12% if there were no predictors. During prophylaxis the recurrence rate was uniformly low (mean 12%) in all risk groups. In high (three or more factors) and intermediate (two factors) risk children prophylaxis provided effective seizure control and reduced the recurrence rate from 80%, or more, to 12% and 50% to 12%, respectively. In children with one risk factor 50% of all recurrences were prevented (25% to 12%). Prophylaxis was ineffective in very low risk children (12% to 12%).

Autret et al, 1990: Adverse effects - (185 children with simple or complex febrile seizures) found that diazepam significantly increased the number of days that children were hyperactive (defined as agitation and ability to keep still) compared with placebo (138 days with diazepam v 34 days with placebo; P less than 0.0003).

Rosman et al, 1993: Adverse effects - 59/153 (39%) children taking intermittent diazepam had adverse effects, including: ataxia; lethargy; irritability; or difficulties with speech, activity level, or sleep. One child taking placebo had a rash.

Knudsen et al, 1996**: *Long term outcomes other than epilepsy*** - no significant difference in full scale, verbal, or performance intelligence quotients (IQ; measured by the Wechsler Intelligence Scale for Children [WISC] general intelligence test), memory, reading tests, and overall scholastic performance at 12 years between intermittent diazepam and diazepam during seizures (absolute results tabulated; P value not significant for all outcomes).

Adverse effects reported in RCTs comparing continuous Phenobarbital (PB) vs. placebo or no treatment (adapted from Mewasingh, 2008)

Study	Population	Adverse effects
Thilothammal et al, 1993	90 children with 2 or more previous simple febrile seizures (60 taking PB v 30 taking placebo)	Adverse effects necessitating withdrawal: 3/60 (5%) PB-treated children had “intolerable” adverse effects (defined as effects persistent for longer than 1 month), including hyperkinetic behaviour, extreme irritability, fussiness, aggressiveness, all of whom withdrew from the study owing to the adverse effects. 1/30 (3.3%) of children taking placebo withdrew for unknown reasons
Camfield et al,	79 children with 1 previous simple	Adverse effects necessitating withdrawal: 4/39 (10%) in both groups withdrew because of

1980	febrile seizure	intolerable adverse effects
Bacon et al, 1981	161 children with 1 previous simple febrile seizure	Negative effects on behaviour: Many parents of children taking PB reported deterioration in behaviour, as did many parents of children taking placebo (absolute numbers and P value not reported); 20% reported slight improvement in some aspects of behaviour when PB was withdrawn
Wolf & Forsythe, 1978	371 children with 1 previous simple febrile seizure (109 taking continuous PB v 142 intermittent PB v 120 no treatment)	Negative effects on behaviour: 46/109 (42%) children taking continuous PB developed a behaviour disorder, usually hyperactivity, compared with 22/120 (18%) having no treatment. Hyperactivity spontaneously disappeared in 52% of children. Continuous PB was prematurely discontinued in 25/46 (54%) of the children with behaviour abnormality (20% of those treated)
Farwell et al, 1990	217 children with at least 1 previous simple febrile seizure	Negative effect on cognition: 2-year follow-up mean IQ, PB v placebo: –7.03 points, 95% CI –11.52 points to –2.5 points; P = 0.0068). 6 months after weaning and discontinuation of PB, mean IQ PB v placebo: –5.2 points, 95% CI –10.5 points to 0.04 points; P = 0.052)
Camfield et al, 1979 (not included in systematic review, additional study)	65 children with 1 previous simple febrile seizure	Negative effects on behaviour (increased fussiness and sleep disturbance classed as transient, dose related, or unacceptable): transient: 8/35 (23%) with PB v 7/30 (23%) with placebo; dose related: 4/35 (11%) with PB v 0/30 (0%) with placebo; unacceptable: 3/35 (9%) with PB v 1/30 (3%) with placebo. Decreased comprehension: Children taking PB had lower scores on memory concentration items on the Stanford–Binet Intelligence scale at 8- to 12-month followup compared with children taking placebo, although the difference between groups was not significant (absolute numbers not reported; P = 0.07).

Continuous sodium valproate vs. placebo or no treatment - Temkin, 2001 identified three RCTs (278 children) comparing sodium valproate versus placebo or no treatment. [26] It found no significant difference between groups in the proportion of children with febrile seizure recurrence. The authors of the review suggest that, if only the small (48 children), placebo-controlled RCT is considered, there is a significant decrease in recurrent febrile seizures with sodium valproate compared with placebo (1/22 [4%] with sodium valproate v 9/26 [35%] with placebo; RR 0.13, 95% CI 0.02 to 0.96, P = 0.01).

The American Academy of Paediatrics, 1999, based on their systematic review (no meta-analysis done), reported that only 4% of children taking valproic acid, as opposed to 35% of control subjects, had a subsequent febrile seizure. Therefore, valproic acid seems to be at least as effective in preventing recurrent simple febrile seizures as phenobarbital and significantly more effective than placebo. They include valproate vs. phenobarbital and/or placebo trials.

GRADE tables:

Table 1

Author(s): Dua T, Hyunh N, Bell G
Date: 2009-08-12
Question: Should Physical methods of temperature reduction vs. Antipyretic drugs be used in children with simple febrile seizures?
Settings:
Bibliography: Mewasingh LD (2008). Febrile seizures. *Clinical Evidence,* (Online). May 22;2008. pii: 0324.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Physical methods of temperature reduction	Antipyretic drugs	Relative (95% CI)	Absolute		
recurrence of febrile seizure - not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

Table 2

Author(s): Dua T, Hyunh N, Bell G
Date: 2009-08-12
Question: Should Antipyretic drugs vs. placebo be used in children with simple febrile seizures?
Settings:
Bibliography: El-Radhi AS, Barry W (2003). Do antipyretics prevent febrile convulsions? *Archives of Diseases in Childhood,* 88:641-2;

Meremikwu M, Oyo-Ita A (2002). Paracetamol for treating fever in children. *Cochrane Database Systematic Reviews,* (2):CD003676.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antipyretic drugs	placebo	Relative (95% CI)	Absolute		
Recurrence of febrile seizure												
2	randomized trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	45/166 (27.1%)	45/174 (25.9%) 0%	RR 1.05 (0.74 to 1.5)	13 more per 1000 (from 67 fewer to 129 more) 0 more per 1000 (from 0 fewer to 0 more)	LOW	CRITICAL
adverse effects												
3[3]	randomized trials	serious[4]	no serious inconsistency	serious[5]	serious[6]	none	9/130 (6.9%)	4/124 (3.2%) 0%	RR 1.84 (0.65 to 5.18)	27 more per 1000 (from 11 fewer to 135 more) 0 more per 1000 (from 0 fewer to 0 more)		CRITICAL

[1] the 2 included studies double blind placebo controlled RCT; drop outs not described; pooled analysis done by self; BMJ clinical evidence describes the systematic review to have weak methods (inadequate search methods difficult to replicate, no inclusion/exclusion criteria); however no additional RCT identified by BMJ clinical evidence.

[2] No explanation was provided.

[3] Meremikwu & Oyo-Ita, 2002, Cochrane review ; analysis 1.2, comparison 1.

[4] The systematic review on antipyretic (both paracetamol and ibuprofen) vs. placebo in simple febrile seizures do not give information on adverse effects. This systematic review compares paracetamol vs. placebo in children with fever.

[5] 95% CI 0.65 - 5.18 (crossing 1 and upper CI more than 2).

[6] one study used ibuprofen and other paracetamol.

Table 3

Author(s): Tarun Dua, Nelly Huynh, Gail Bell
Date: 2009-08-13

Question: Should Intermittent diazepam (during episodes of fever) vs. placebo be used in children with simple febrile seizures ?

Settings:

Bibliography: Masuko AH et al (2003). Intermittent diazepam and continuous phenobarbital to treat recurrence of febrile seizures: a systematic review with meta-analysis. *Arquivos de Neuro-Psiquiatria,* 61:897-901. Epub 2004 Jan 6.

Knudsen FUet al (1996). Long term outcome of prophylaxis for febrile convulsions. *Archives of Diseases in Childhood,* 74:13-8. (single RCT on long term outcome)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent diazepam (during episodes of fever)	placebo	Relative (95% CI)	Absolute		
Recurrence of febrile seizure												
4[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	44/393 (11.2%)	68/398 (17.1%) 0%	OR 0.60 (0.4 to 0.9)	61 fewer per 1000 (from 14 fewer to 95 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
adverse effects - not reported[4]												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Risk of subsequent epilepsy (follow-up 14 years)												
1[5]	randomized trials	very serious[6]	no serious inconsistency	serious[7]	serious[8]	none	1/152 (0.7%)	1/137 (0.7%) 0%	RR 0.9 (0.06 to 14.27)	1 fewer per 1000 (from 7 fewer to 97 more) 0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL

[1] Masuko et al, 2003.
[2] Autret et al, 1990 described as randomized but description not provided; Mosquera et al, 1987 not sure if it was double blinded, Rosman et al, 1993 drop outs 25% in diazepam group and 27% in placebo group, one of the included RCT reported poor compliance in children taking diazepam, which was significantly different from those on placebo.
[3] I square value not provided with meta-analysis but the test for heterogeneity statistically significant. The mode, dose, and frequency of administration of diazepam varied in each RCT.
[4] The systematic review does not provide information on adverse effects. On assessment of individual papers, two of the included RCTS reports information on adverse events (Autret et al, 1990; Rosman et al, 1993). In addition, a study carried out after the systematic review (Pavlidou et al, 2006)) also provides some information on adverse events. For details refer to individual description of studies.
[5] Knudsen et al, 1996.
[6] Quasi-randomized study, assigning to groups depending on whether the child was admitted on odd or even date; outcome assessment not masked; follow up rate 93.4%.
[7] Single study.
[8] the 95% confidence interval very wide and includes both no effect and appreciable benefit or appreciable harm.

Table 4

Author(s): Tarun Dua, Nelly Huynh, Gail Bell

Date: 2009-08-13

Question: Should Intermittent clobazam (during episodes of fever) vs. placebo be used in children with simple febrile seizures?

Management of febrile seizures

Settings:

Bibliography: Rose W, Kirubakaran C, Scott JX (2005). Intermittent clobazam therapy in febrile seizures. *Indian Journal of Pediatrics,*72:31-3.

Bajaj AS et al (2005). Intermittent clobazam in febrile seizures: an Indian experience. *Journal of Paediatric Neurology,* 3:19-23.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent clobazam (during episodes of fever)	placebo	Relative (95% CI)	Absolute		
recurrence of febrile seizure												
2[1]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/0 (0%)	0/0 (0%) 0%	not pooled[4]	not pooled not pooled	VERY LOW	CRITICAL
Adverse effects (ataxia) (follow-up mean 9.9 months)												
1[5]	randomized trials	very serious[2]	no serious inconsistency[5]	serious[5]	very serious[6]	reporting bias	5/60 (8.3%)	0/48 (0%) 0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL

[1] 2 RCTS, no pooled estimate available.

[2] Rose et al, 2005: randomized, double blind, drop outs not clear from abstract, check the full text article, the study randomized children and analysed episodes of fever, not clear if the authors adjusted for this (however it is likely that results will remain significant after adjustment). Bajaj et al, 2005: method of randomisation not reported, analysis not intention to treat, drop outs not clear.

[3] 40 children included in first study and 60 children in second study (however both studies analysed febrile episodes which are more than 200).

[4] Rose et al, 2005 - 40 children with 1 or more episodes of febrile seizure compared clobazam given during episodes of fever versus placebo. The children had 108 episodes of fever over a mean 9.9 months; 60 episodes were treated with clobazam and 48 with placebo. Clobazam given during a febrile episode significantly reduced the rate of seizure recurrence compared with placebo (6/48 [12%] episodes with placebo v 1/60 [2%] episodes with clobazam; P = 0.01). Bajaj et al, 2005 - 60 children who completed the study, aged 6 months to 5 years, presenting with 1 or more episodes of febrile seizure. The children had 312 episodes of fever over a period of 6 months; 151 episodes were treated with clobazam and 161 with placebo. Clobazam given during a febrile episode significantly reduced the recurrence of seizures compared with placebo (recurrence of seizures with febrile episodes: 9/30 [30%] people with clobazam v 25/30 [83%] people with placebo; P less than 0.001).

[5] Single study, Rose et al, 2005.

[6] 40 children in study who were randomized, however, fever episodes analysed (total 108 episodes of fever).

Table 5

Author(s): Tarun Dua, Nelly Huynh, Gail Bell
Date: 2009-08-14
Question: Should Continuous phenobarbital vs. placebo be used in children with simple febrile seizures?
Settings:
Bibliography: Temkin NR (2001). Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia,* 42:515-24.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous phenobarbital	placebo	Relative (95% CI)	Absolute		
Recurrence of febrile seizure												
8	randomized trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	90/483 (18.6%)	184/492 (37.4%) 0%	RR 0.51 (0.32 to 0.82)	183 fewer per 1000 (from 67 fewer to 254 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	ÅOOO VERY LOW	CRITICAL
adverse effects necessitating withdrawal												
2[3]	randomized trials	no serious limitations[4]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[6]	7/99 (7.1%)	5/69 (7.2%)	RR 1.13 (0.36 to 3.48)[7]	9 more per 1000 (from 46 fewer to 180 more)	ÅÅOO LOW	CRITICAL
adverse effect (negative effect on behaviour)												
2[8]	randomized trials	very serious[9]	serious[10]	no serious indirectness	no serious imprecision	reporting bias[6]	54/144 (37.5%)	29/150 (19.3%) 0%	RR 1.95 (1.33 to 2.87)	184 more per 1000 (from 64 more to 362 more) 0 more per 1000 (from 0 more to 0 more)	ÅOOO VERY LOW	CRITICAL
adverse effect (negative effect on cognition) (follow-up 2 years; Better indicated by lower values)												
1[11]	randomized trials	no serious limitations[4]	no serious inconsistency[12]	serious[12]	no serious imprecision	reporting bias[6]	108	109	-	MD 7.03 lower (11.52 to 2.5 lower)[13]	ÅÅOO LOW	CRITICAL
risk of subsequent epilepsy (follow-up mean 6.3 years)												
1[9]	randomized trials	serious[9,14]	no serious inconsistency[12]	serious[12,15]	serious[16]	none	7/116 (6%)	1/126 (0.8%) 0%	RR 7.6 (0.95 to 60.87)	52 more per 1000 (from 0 fewer to 475 more) 0 more per 1000 (from 0 fewer to 0 more)	ÅOOO VERY LOW	CRITICAL

[1] 3/8 studies, not placebo controlled, drop outs not clear from systematic review, but the comment is that most studies did not assess compliance (to check individual studies).

[2] I square not provided, however tests for statistical heterogeneity was found significant. Visual investigation of forest plot also suggests heterogeneity. Doses of phenobarbital varied across studies.

[3] Thilothammal et al, 1993; Camfield et al, 1980.

[4] systematic review did not assess adverse effects, data presented from individual studies.

[5] Sample size 168.
[6] not reported in other included studies.
[7] Thilothammal et al, 1993: Adverse effects necessitating withdrawal: 3/60 (5%) PB-treated children had "intolerable" adverse effects (defined as effects persistent for longer than 1 month), including hyperkinetic behaviour, extreme irritability, fussiness, aggressiveness, all of whom withdrew from the study owing to the adverse effects. 1/30 (3.3%) of children taking placebo withdrew for unknown reasons. Camfield et al, 1980 - 4/39 (10%) in both groups withdrew because of intolerable adverse effects.
[8] Bacon et al, 1981; Wolf et al, 1978.
[9] Wolf et al, 1989 not placebo controlled, drop outs not known.
[10] I square 65%.
[11] Farwell et al, 1990.
[12] single study.
[13] Camfield et al, 1979 (not included in systematic review, additional study) - Children taking PB had lower scores on memory concentration items on the Stanford-Binet Intelligence scale at 8- to 12-month followup compared with children taking placebo, although the difference between groups was not significant (absolute numbers not reported; P = 0.07).
[14] randomized, outcome assessment and drop out NK, to check original study.
[15] includes both simple and complex febrile seizure.
[16] 95% CI very wide and lower confidence limit crosses a risk of 2.

Table 6

Author(s): Tarun Dua, Nelly Huynh, Gail Bell
Date: 2009-08-14
Question: Should Continuous valproate vs. placebo be used in children with simple febrile seizures?
Settings:
Bibliography: Temkin NR (2001). Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia,* 42:515-24.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous valproate	placebo	Relative (95% CI)	Absolute		
Recurrence of febrile seizure												
3	randomized trials	very serious[1,2]	serious[3]	no serious indirectness	serious[4]	none	29/102 (28.4%)	34/114 (29.8%)	RR 0.74 (0.24 to 2.23)	78 fewer per 1000 (from 227 fewer to 367 more)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
adverse effects - not measured[5]												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
risk of subsequent epilepsy - not reported												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

[1] 2/3 studies not placebo controlled.

[2] American Academy of Paediatrics, 1999 practice parameter systematic review included valproate vs. phenobarbital/ vs. placebo studies. One of the included studies in that review (Wallace and Smith, 1980) is not included in Temkin, 2001 systematic review. Reason for exclusion not clear.

[3] I square not provided, however tests for statistical heterogeneity was found significant. Visual investigation of forest plot also suggests heterogeneity.

[4] 95% CI crossing 1 and upper CI more than 2.

[5] There are known rare, serious adverse effects of sodium valproate include hepatotoxicity and haematological toxicity. Although valproate hepatotoxicity may be dose dependent, it can, more rarely, be an idiosyncratic phenomenon — which means that it is often irreversible and difficult to predict on the basis of laboratory monitoring. Blood disturbances can also be dose dependent, with direct bone marrow suppression leading to aplastic anaemia or peripheral cytopenia affecting one or more cell lines, or even fatal bone marrow failure.

Table 7

Author(s): Tarun Dua, Nelly Huynh, Gail Bell

Date: 2009-08-14

Question: Should Continuous phenobarbital vs. Continuous valproate be used in children with simple febrile seizures?

Settings:

Bibliography: Masuko AH et al (2003). Intermittent diazepam and continuous phenobarbital to treat recurrence of febrile seizures: a systematic review with meta-analysis. *Arquivos de Neuro-Psiquiatria,* 61:897-901. Epub 2004 Jan 6.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous phenobarbital	Continuous valproate	Relative (95% CI)	Absolute		
Recurrence of febrile seizure (follow-up mean 23 months)												
1	randomized trials	no serious limitations[1]	no serious inconsistency[2]	serious[2]	very serious[3]	none	1/22 (4.5%)	4/21 (19%)	RR 0.24 (0.03 to 1.96)	145 fewer per 1000 (from 185 fewer to 183 more)	ÅOOO VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
adverse effects - not measured												

0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL[4]
risk of subsequent epilepsy - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

[1] check drop out rate and outcome assessment from the original paper.

[2] single study.

[3] sample size less than 100, 95% CI wide with no effect and appreciable benefit.

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From evidence to recommendations

<table>
<tr><th>Factor</th><th colspan="4">Explanation</th></tr>
<tr><td>Narrative summary of the evidence base</td><td colspan="4">Febrile seizures are defined as simple if they are generalized, often tonic-clonic, self-limiting, of short duration (<15 minutes), without any after effects, and do not recur within the next 24 hours. Febrile seizures are defined as complex if they have longer duration (>15 minutes), or have focal features, or if they recur within 24 hours (multiple seizures).

Although no data on this is available regarding the capacity of non-specialist health care providers from low-and middle-income countries (LAMIC) health care settings, there are clinical criteria to differentiate simple from complex febrile seizure.

In simple febrile seizures, local standards for diagnosis and management of fever should be followed.
<table>
<tr><td>Intervention/Comparator</td><td>Recurrence of febrile seizure</td><td>Adverse effects</td><td>Risk of subsequent epilepsy</td></tr>
<tr><td>Physical methods of temperature reduction vs. antipyretic drugs/placebo</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Antipyretic drugs vs. placebo</td><td>2 RCTs, No significant effect

RR 1.05 (0.74-1.50)

No difference</td><td>No significant difference, very wide confidence intervals

(The evidence is inconclusive and so it is not possible to determine</td><td>-</td></tr>
</table>
</td></tr>
</table>

			if there is a clinically important difference)	
	Intermittent diazepam vs. placebo or no treatment	4 RCTs, OR 0.6 (0.4-0.9) favouring active treatment	Not reported by review, from individual studies - associated with increased hyperactivity, lethargy, irritability, difficulties in speech, activity level or sleep	Single RCT, no significant difference RR 0.9 (0.06 -14.27) (self calculation) (very wide CI)
	Intermittent clobazam vs. placebo or no treatment	2 RCTs , RR 0.31 (0.18-0.55) (self calculation) favouring active treatment	Significantly increased ataxia in one study	-
	Intermittent vs. continuous anticonvulsant	-	-	-
	Continuous Phenobarbital vs. placebo or no treatment	Statistically significant difference RR 0.51 (0.32-0.82), favouring active treatment	Adverse effect necessitating withdrawal (may be significant difference in one study, other study - no significant difference) (RR 1.13 (0.36-3.48); negative effect on	Single study, RR 7.6 (0.95-60.87) no difference, wide CI

			behaviour ((may be significant difference in one study, other study - no significant difference) 1.95 (1.33-2.87); statistically significant negative effect on cognition	
	Continuous valproate vs. placebo or no treatment	No significant difference RR 0.74 (0.24-2.23)	-	-
	Continuous Phenobarbital vs. continuous valproate	No significant difference RR 0.24 (0.03-1.96)	-	-
	In LAMIC settings, febrile seizures presenting to the health facilities are often complex. Complex febrile seizures (CFS) indicate entities with variable etiology, semiology, and prognosis. Therefore, treatment depends upon the etiologic and nosographic picture. A CFS may result from an acute disorder of the CNS (such as cerebral malaria, bacterial meningitis, encephalitis) or could be simply a prolonged febrile seizure. Admission is recommended for observation because of the wide variability of conditions underlying this event. Search for underlying etiology is recommended in case of CFS. The risk of bacterial meningitis in children presenting with fever and seizure is about 3% and in a complex seizure about 9%. Children with following features - at least 3 days of illness, seen by GP in previous 24 hours, drowsiness at home, vomiting at home, CFS, petechaie, suspected nuchal rigidity, bulging fontanelle, and focal neurological signs - have an increased risk of meningitis. The vast majority of children who present with febrile seizures do not develop epilepsy. However,			

<table>
<tr><td></td><td colspan="4">complex febrile seizures are associated with an increased risk of epilepsy. There are other risks factors for epilepsy, including neurological abnormality, family history of epilepsy, and short duration of fever (<1hr) before the seizure. Children without any risks factors have a 2.4% chance of developing a febrile seizure by 25 yrs compared with 1.4% for the general population. Children with a history of at least 1 complex feature, a neurological abnormality, and a family history have a 10% risk of developing epilepsy by the age of 7. Prolonged febrile seizures increase the incidence of epilepsy to 21%. For children with all 3 features of a complex febrile seizure, the risk increases to 49%.

In CFS, prophylactic therapy might be advocated because of concerns of aggravation and epilepsy. However, favourable outcomes need to be balanced with the risks associated to anticonvulsant therapy. Prophylactic treatment is considered in case of recurrent prolonged febrile seizures.</td></tr>
<tr><td rowspan="4">Summary of the quality of evidence</td><td>Intervention/Comparator</td><td>Recurrence of febrile seizure</td><td>Adverse effects</td><td>Risk of subsequent epilepsy</td></tr>
<tr><td>Physical methods of temperature reduction vs. antipyretic drugs/placebo</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Antipyretic drugs vs. placebo</td><td></td><td></td><td>-</td></tr>
<tr><td>Intermittent diazepam vs. placebo or no treatment</td><td>Very low</td><td></td><td>Very low</td></tr>
</table>

	Intermittent clobazam vs. placebo or no treatment	Very low	Very low	-
	Intermittent vs. continuous anticonvulsant	-	-	-
	Continuous Phenobarbital vs. placebo or no treatment	Very low	Low to very low	low
	Continuous valproate vs. placebo or no treatment	Very low	-	-
	Continuous Phenobarbital vs. continuous valproate	moderate	-	-
Balance of benefits versus harms	Intermittent antipyretics may be no more effective than placebo in treating episodes of fever to prevent seizure recurrence in children with one or more previous simple febrile seizures. Intermittent anticonvulsant (diazepam or clobazam) are may be more effective at reducing the risk of febrile seizure recurrence in children with a history of simple or complex febrile seizures. However diazepam has been associated with increased hyperactivity, lethargy, irritability, and with difficulties with speech, activity level, or sleep. Clobazam is also associated with adverse effects such as ataxia. Phenobarbital may be more effective at reducing febrile seizure recurrence in children with a history of simple or complex febrile seizures. Phenobarbital is may be associated with cognitive impairment, and with behavioural problems including hyperactivity, irritability, and			

	aggression. Continuous sodium valproate may be no more effective at reducing febrile seizure recurrence in children with a history of simple or complex febrile seizures. Serious adverse events which may be associated with sodium valproate include hepatotoxicity, and haematological toxicity, both of which may occasionally be fatal. The evidence is inconclusive whether phenobarbital is more effective than sodium valproate at reducing the proportion of children with febrile seizure recurrence. Intermittent diazepam or continuous phenobarbital may be no more effective at reducing the risk of subsequent epilepsy in children with febrile seizures.
Values and preferences including any variability and human rights issues	For febrile seizures, prophylactic therapy is advocated by some because of the concerns that such seizures lead to additional febrile seizures, to epilepsy, and perhaps even to brain injury. Moreover, they note the potential for such seizures to cause parental anxiety. Addressing parental anxiety should a key part of the management of febrile seizures, as parents' (unspoken) worry with a first seizure is that their child might have died.
Costs and resource use and any other relevant feasibility issues	The non-specialist health care provider can be trained to recognize and manage febrile seizures.
Final recommendation(s) Children with simple febrile seizures can be diagnosed and managed by non-specialist health care providers in low and middle income countries. In simple febrile seizures, local standards for diagnosis and management of fever should be followed and children should be observed for 24 hours. Integrated Management of Childhood Illnesses (IMCI) guidelines should be used for management of fever.	

Strength of recommendation: STRONG

Prophylactic treatment with intermittent antipyretics, intermittent anticonvulsant (diazepam or clobazam), or continuous anticonvulsant (phenobarbital or valproic acid) should not be considered for simple febrile seizures.
Strength of recommendation: STANDARD

For children with complex febrile seizures (CFS), observation within inpatient setting is recommended as these may result from an acute disorder of the central nervous system or could be simply a prolonged febrile seizure. Therefore they should be referred to second level care. Investigations such as blood tests, lumbar puncture to determine the presence of underlying etiology is recommended in case of CFS depending on the local context and other clinical symptoms.
Strength of recommendation: STRONG

Prophylactic intermittent diazepam may be considered in the treatment of recurrent or prolonged complex febrile seizures (CFS).
Strength of recommendation: STANDARD

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Mewasingh LD. Febrile seizures. Clinical Evidence 2010;11:324.

Offringa M, Newton R. Prophylactic drug management for febrile seizures in children. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD003031. DOI: 10.1002/14651858.CD003031.pub2. (New, published in Issue 4, 2012.)

Management of febrile seizures