HIGHLIGHTS IN GENERAL PEDIATRICS AND PEDIATRIC EMERGENCY CARE: 2021

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HIGHLIGHTS IN GENERAL PEDIATRICS AND PEDIATRIC EMERGENCY CARE: 2021

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What Pediatricians Need to Know About the CDC Guideline on the Diagnosis and Management of mTBI

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Pediatric traumatic brain injury (TBI) is a growing health concern, with over half a million TBI-related emergency department (ED) visits annually. However, this is likely an underestimate of the true incidence, with many children presenting to their pediatrician. The Centers for Disease Control and Prevention (CDC) published a guideline on the diagnosis and management of pediatric mild traumatic brain injury (mTBI). We outline key points and a decision checklist for pediatricians based on this evidence-based guideline.

Keywords: guideline, concussion, traumatic brain injury, concussion diagnosis, concussion management

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BACKGROUND

Pediatric traumatic brain injury (TBI) is a growing public health concern. In 2013, there were an estimated 641,935 TBI-related emergency department (ED) visits, 17,930 TBI-related hospitalizations, and 1,484 TBI-related deaths among children aged 0–14 years in the United States (1). These data underestimate the true burden as the majority of pediatric patients with a mild traumatic brain injury (mTBI), which includes concussion, may seek care from an outpatient clinic or not seek care at all. In a study of point of entry within the Children's Hospital of Philadelphia system, Arbogast et al. found that 82% of patients had their first concussion-related visit within primary care, with only 12% entering care through the ED (2). With legislation in all 50 states requiring evaluation or diagnosis prior to return to play after a sports-related mTBI in children and adolescents, pediatricians may see a growing number of children in their offices with such injuries. These statistics point to the necessity of evidence-based recommendations for pediatricians. While mTBI guidelines are available for use in the adult population, comprehensive evidence-based guidelines for the diagnosis and management of pediatric mTBI have not been developed in the United States (3).

THE CDC GUIDELINE ON DIAGNOSIS AND MANAGEMENT OF MTBI AMONG CHILDREN

The Centers for Disease Control and Prevention (CDC) released evidence-based clinical recommendations on the diagnosis and management of pediatric mTBI. The *CDC Guideline on the Diagnosis and Management of Mild Traumatic Brain Injury Among Children* offers practical recommendations for pediatricians (and other specialties) to improve outcomes of children 18 years of age and younger. CDC used a broad clinical and functional definition of pediatric mTBI;

that is, studies informing the Guideline included children described in the literature as having an mTBI by historical definitions, encompassing Glasgow Coma Scale scores of 13–15 with or without the complication of intracranial injury on neuroimaging, and regardless of the potential need for a hospital admission and/or neurological intervention (3). The Guideline provides: (1) diagnostic recommendations regarding the utility of head imaging, symptom scales, cognitive testing, and biomarkers; (2) prognostic recommendations that focus on counseling, assessing history, and risk, tools to track recovery, and interventions for patients with poor prognosis; and (3) management and treatment recommendations that focus on education, counseling, emotional support, return to activity and school, and management of specific symptoms.

The Guideline was developed through a rigorous federal advisory scientific process with expert input from a wide variety of perspectives (clinical providers, researchers, patients) and specialties (pediatrics, neurology, emergency medicine, sports medicine). Clinical questions were identified, and a systematic review of the literature was conducted. Evidence was rated using a modified Grading of Recommendation Assessment Development and Evaluation (GRADE) approach and used to inform recommendations on the diagnosis, prognosis, and management of mTBI in the context of scientific principles, related evidence, and expert inference.

The Guideline puts forth 19 sets of recommendations organized by clinical focus area. Recommendations are categorized by obligation (must, should, may) addressing the following topics: imaging, symptom scales, cognitive testing, the use of standardized testing for diagnosis, relevant history, and risk factor assessment, monitoring after injury, counseling regarding prognosis, and referral for further treatment. In this Perspective, we highlight recommendations from the CDC Guideline that are deemed to be the most relevant for the practicing pediatrician, prioritized by CDC for dissemination. In particular, we emphasize recommendations that apply to longer-term symptom management and return to activity, such as to school and sports, for pediatricians who not only see children at an initial visit for diagnosis, but also engage in regular follow-up—which can be uniquely different from other providers, such as emergency medicine practitioners. See **Figure 1** for a checklist for providers on steps to take in diagnosing and managing mTBI in children.

KEY RECOMMENDATIONS FOR PEDIATRICIANS

Diagnosis and Management

Many tools to assess mTBI symptoms, prognosis, and recovery exist, but few are validated in the pediatric population, and none should be used in isolation. Initial evaluation consists of a combination of thorough history including screening for known risk factors for poor prognosis and the use of validated and age-appropriate tools for diagnosis. CDC recommends that this include a validated, age-appropriate symptom rating scale as a component [e.g., Post-Concussion Symptom Scale from ImPACT (4), Health Behavior Inventory (5), Post-Concussion Symptom Inventory (6); see **Figure 1**]. The use of computerized cognitive testing (e.g., ImPACT) may be helpful as an adjunctive test for diagnosis, but should not be used in isolation. A combination of tools may be useful in assessing recovery including validated symptom scales, cognitive testing, and balance testing. Going beyond the specific tools recommended in the Guideline, the National Academies report on sports-related concussions in youth provides additional information about tools that are available for use in the sport context (e.g., the Sport Concussion Assessment Tool for the sideline evaluation of athletes) (7). Clinicians can base selection of symptom rating scales and tools on the age of the child or adolescent being assessed, as well as the context of the injury. For example, Gioia et al. provide a review of clinical tools and symptom scales that are particularly useful for assessing student-athletes in the sports context (8).

Once the diagnosis of mTBI is made, pediatricians should counsel the child and his/her family that the majority (70–80%) of children recover within 1–3 months without difficulty. Education for the child and his/her family should include warning signs of more serious injury, how to prevent further injury (e.g., gradual return to activities), how to monitor symptoms, management of recovery through rest, and instructions on returning to cognitive and physical activity/recreation. By providing education and reassurance, one may avoid prolonged symptoms. **Figure 1** provides further guidance on information to provide patients and their families (see *Counsel* step).

Pediatricians should recommend a brief period of rest (2–3 days) from physical and cognitive activities, which may be followed by symptom-limited activity. Too much rest beyond this period may worsen a child's symptoms and prolong recovery. Cognitive activity should be reintroduced gradually followed by physical activity, both of which should follow a gradual return to learn or play protocol with close monitoring for exacerbation of symptoms. A child may return to full pre-injury activity when symptom-free at rest and with stepwise progression of physical exertion. Active recovery may decrease the presence of post-concussive symptoms in those children who have prolonged symptoms (3). Symptomatic treatment for headache may include non-opioid analgesics such as acetaminophen or ibuprofen.

When to Refer for Imaging

CDC recommends that pediatricians should not routinely image a child presenting with suspected mTBI (see *Assess* step in **Figure 1**). Rather, clinicians should use validated clinical decision rules to determine the need for imaging based on factors that increase risk for injury (e.g., age <2 years, vomiting, loss of consciousness, severe or worsening headache, amnesia), and counsel the patient and family regarding the risks associated with imaging. However, pediatricians should refer a child for imaging if the presenting symptom is severe headache with additional risk factors or worsening headache

Abbreviations: CDC, Centers for Disease Control and Prevention; TBI, traumatic brain injury; mTBI, mild traumatic brain injury; ED, emergency department; CT, computed tomography.

CDC PEDIATRIC mTBI GUIDELINE
Checklist

CDC HEADS UP
SAFE BRAIN. STRONGER FUTURE.

For healthcare providers treating children 18 years of age and younger

HEALTHCARE PROVIDERS SHOULD:

ASSESS.

Conduct a physical examination to identify findings that:

- Suggest more severe TBI (e.g., hemotympanum, pupillary asymmetry).
- May impact management of mTBI (e.g., concurrent injuries or baseline deficits, oculomotor dysfunction).
- Suggest other contributions to symptoms (e.g., dehydration, cervical tenderness, scalp hematoma).

Do not image routinely (including CT & MRI).

- Use validated clinical decision rules predicting risk for more severe injury to determine need.

Assess symptoms using validated scales. Consider cognitive and balance testing.

Conduct a history to identify risk factors for poor prognosis using validated prediction rules.

A combination of risk factors that may indicate need for neuroimaging include:

- Age < 2 years old
- Recurrent vomiting
- Loss of consciousness
- Severe mechanism of injury
- Severe or worsening headache
- Amnesia
- Non-frontal scalp hematoma
- Glasgow Coma Score < 15
- Clinical suspicion for skull fracture

Examples of validated scales include, but aren't limited to:

- Post-Concussion Symptom Scale
- Health and Behavior Inventory
- Post-Concussion Symptom Inventory
- Acute Concussion Evaluation

COUNSEL.

Provide information about:

- Warning signs that injury may be more serious.
- Typical recovery course.
- How to prevent further injury.
- Gradual re-introduction of activity that does not worsen symptoms.
- The need for social and emotional support.

Offer clear instructions (preferably verbal and written) on return to activity, including school and sports, customized to the patient's symptoms.

- After a few days of rest (2-3 days), begin light activity & then gradually re-introduce regular activities (not inclusive of sports) that do not significantly worsen symptoms.
- Assess school-related needs & monitor progress in collaboration with parents and school professionals.
- Once back to regular non-sports activities (including school), patient can begin return to sports using a standard progression with gradually increasing levels of physical exertion.
- No return to contact sports activity until symptom-free with exertion (including without the use of pain medication).

Factors associated with poor prognosis:

- Older age (older children/adolescents) or Hispanic ethnicity
- Lower socio-economic status
- History of intracranial injury
- Premorbid histories of mTBI or increased pre-injury symptoms
- Neurological or psychiatric disorder
- Learning difficulties or lower cognitive ability
- Family and social stressors

Parents should watch for warning signs:

- A headache that gets worse & does not go away
- Significant nausea or repeated vomiting
- Increased confusion, restlessness, or agitation
- Slurred speech, drowsiness, or inability to wake up
- Weakness, numbness, or decreased coordination
- Loss of consciousness, convulsions, or seizures

Steps in a return to play progression generally include:

Step 1: Return to regular non-sports activities
Step 2: Light aerobic exercise
Step 3: Sport-specific exercise
Step 4: Non-contact training drills
Step 5: Full contact practice
Step 6: Return to sport

REFER.

Identify and tailor treatment plans/referrals to address:

- Acutely worsening symptoms → consider neuroimaging.
- Chronic headache → non-opioid analgesia (monitor for overuse), multi-disciplinary evaluation.
- Vestibulo-ocular dysfunction → vestibular rehabilitation.
- Worsening sleep problem → sleep hygiene, sleep specialist.
- Cognitive impairment → treatment directed at etiology, neuropsychological evaluation.
- Emotional dysfunction → psychotherapeutic evaluation and treatment.

Refer patients whose symptoms do not resolve as expected with standard care after 4-6 weeks.

CDC

To view the full set of recommendations from the CDC Pediatric mTBI Guideline, visit www.cdc.gov/HEADSUP.

FIGURE 1 | Checklist for diagnosing and managing mild traumatic brain injury (mTBI) in children.

for imaging to assess for possible intracranial injury. There is moderate risk for a clinically important intracranial injury (e.g., hemorrhage) when a child presents with a mild injury (Glasgow Coma Score 13–15) and a severe or worsening headache. Validated clinical decision rules can help to identify those children at higher risk for a clinically important intracranial injury, and who should be referred for head CT (see **Figure 1** for factors that assist in determining need for imaging) (9).

When to Refer for Further Treatment

If symptoms do not resolve within 4–6 weeks, further assessment and intervention may be needed. There may be risk factors present for prolonged symptoms; these can be identified when obtaining the patient's past medical and family history. Children who have a history of TBI, neurological, or psychiatric disorder, learning difficulties, or family or social stressors may be at risk for delayed recovery. Pediatricians may use validated prediction rules that combine information about such risk factors to identify children at highest probability for persistent symptoms (see **Figure 1** for factors associated with delayed recovery). These children and their families may be counseled accordingly, and may warrant earlier referral to a specialized clinic for close follow-up.

The majority of children will return to baseline within 1–3 months. Persistent symptoms may require specialized intervention. Children with persistent vestibulo-oculomotor dysfunction may benefit from vestibular rehabilitation. Persistent cognitive impairment should also be treated with specific consideration of the presumed etiology. Formal neuropsychological evaluation may help in determining the etiology and appropriate treatment (see *Refer* step in **Figure 1**).

CONCLUSION

CDC offers tools to assist providers in implementing the Guideline recommendations in clinical practice, as well as in assisting children in returning to activity/play and school. The CDC HEADS UP materials for healthcare providers (www.cdc.gov/headsup/providers) includes free online training with continuing education credits available, as well as the provider checklist, diagnostic and assessment tools, discharge instructions, and guidance on return to play and return to learn protocols (10). Integration of recommendations using prompts and alerts within the electronic health record could also assist pediatricians with implementation at the point of care, particularly with return to learn and return to play recommendations (11).

AUTHOR CONTRIBUTIONS

MC and TH drafted the initial manuscript, and reviewed and revised the manuscript. AG reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SYSTEMATIC REVIEW
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Symptomatic Management of Febrile Illnesses in Children: A Systematic Review and Meta-Analysis of Parents' Knowledge and Behaviors and Their Evolution Over Time

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Recommendations to guide parents' symptomatic management of febrile illnesses in children have been published in many countries. The lack of systematic appraisal of parents' knowledge and behaviors and their evolution over time precludes an analysis of their impact and identification of targets for future educational messages. We systematically searched for studies published between 1980 and 2016 that reported a quantitative evaluation of knowledge and behaviors of >50 parents for managing fever in children. We used MEDLINE and tracked related articles, citations and co-authors personal files. Study selection and data extraction were independently performed by two reviewers. For each item of knowledge and behaviors, we calculated mean frequencies during the first and last quinquennials of the studied period and assessed temporal trends with inverse-variance weighted linear regression of frequencies over years. We observed substantial methodological heterogeneity among the 62 included articles (64 primary studies, 36,791 participants, 30 countries) that met inclusion criteria. Statistically significant changes over time were found in the use of rectal (98 to 4%) and axillary temperature measurement (1–19%), encouraging fluid intake (19–62%), and use of acetylsalicylic acid (60 to 1%). No statistically significant change was observed for the

accurate definition of fever (38–55%), or the use of acetaminophen (91–92%) or ibuprofen (20–43%). Parents' knowledge and behaviors have changed over time but continue to show poor concordance with recommendations. Our study identified future targets for educational messages, including basic ones such as the definition of fever.

Keywords: health behavior, child, fever, parents, meta-analysis

INTRODUCTION

Fever, one of the most common symptoms of illness in children, is frequently caused by self-limited viral infections. Despite not being harmful in itself, fever may be associated with pain and discomfort (1, 2). However, fever is often the first cause for medical consultation in childhood, and the main source of drug exposure in pediatrics (1–12). Although widely used and potentially helpful to relieve discomfort, antipyretic medications are not without possible side-effects. Several studies have highlighted that parents' knowledge and behaviors are largely dominated by "fever phobia," the undue anxiety about fever, more than 40 years after it was first described (1, 5–16). Notably, parents are often scared by the rare situations in which fever is the first sign of a serious illness, such as severe bacterial infection (17), or is associated with seizures (1, 5).

Recommendations to guide parents' symptomatic management of febrile illnesses in children have been published by several national health agencies and medical societies in a number of different countries (2, 18–24). Generally, recommendations address (**Table 1**): (i) temperature measurement method [rectally (18, 19, 23, 24), orally (18, 19, 23, 24), auricular (2, 18, 19, 21–23), or axillary (2, 18, 19, 21–24)]; (ii) the definition of fever [temperature $\geq$38°C (2, 3, 18, 19, 23, 24)]; (iii) when to start antipyretics (2, 18, 19, 21–24); (iv) physical treatments [encouraging fluid intake (2, 18, 19, 22–24), light clothing (2, 18, 19, 22–24), adjust room temperature (19, 23, 24)]; and (v) drug treatments [monotherapy with acetaminophen (2, 3, 18, 19, 21–24) or ibuprofen (2, 3, 18, 19, 22–24)]. The lack of systematic appraisal of temporal changes in parents' knowledge and behaviors was recently highlighted as an obstacle to evaluate the impact of recommendations (25). Such a systematic appraisal could help identify the knowledge and behaviors that differ from recommendations in order to develop future educational messages (25).

We aimed to systematically review studies on parents' knowledge and behaviors for the management of febrile illnesses in children, and to assess whether they have changed over time.

METHODS

We conducted a systematic review following the methodology proposed by the Centre for Reviews and Dissemination (26) and reported it using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (27) (checklist in Appendix 1 in **Supplementary Material**).

Search Strategy and Selection Criteria

We aimed to include all studies performed since 1980 [date of the first publication on fever phobia (6)] that reported quantitative data on knowledge and behaviors regarding fever in children (aged <18 years) of >50 (arbitrary) parents. We searched for study reports published from January 1, 1980 to September 1, 2016, in MEDLINE via PubMed, with the following search strategy: ("behavior" [MeSH Term] OR "attitude" [MeSH Term] OR "analgesics" [MeSH Term] OR "acetaminophen/therapeutic use" [Mesh Term]) AND ("child" [MeSH Term] OR "infant" [MeSH Term]) AND "fever" [MeSH Term] AND ("1980/01/01" [PDAT]: "2016/09/01" [PDAT]). We also searched Science Citation Index and Google Scholar for studies citing the included studies and examined the first 50 "related articles" of included studies in PubMed. Finally, we hand-searched the reference lists of included studies, as well as personal files of the international network of co-authors. We included studies published in English, French, German, Italian, and Spanish.

Two review authors (NB, NH) independently excluded clearly ineligible studies based on their titles and abstracts. They then retrieved the full text of potentially eligible articles to independently evaluate them for inclusion. Another review author (MC) acted as arbiter in case of discrepancies between them.

Data Extraction

For each included study, two review authors (NB, NH) independently extracted study characteristics (year of publication and of the study, general methodology of the survey, country, sample size) and the frequency reported for the following knowledge and behaviors, which were selected based on their citation in published recommendations (**Table 1**): temperature measurement method (rectally, orally, auricular, or axillary), definition of fever, physical treatments (encouraging fluid intake, light clothing, adjust room temperature, bathing, or sponging) and drug treatments (monotherapy, use of acetaminophen, ibuprofen, or acetylsalicylic acid).

Risk of Bias Assessment

For observational studies, no tool has been validated to evaluate the risks of bias and threat to generalizability for conducting a systematic review. After discussions among the authors, the following criteria were selected to assess these risks: single- vs. multi- center recruitment, hospital-based vs. broader recruitment of participants, and theoretical knowledge and behaviors (case scenarios) vs. observed ones for a current/recent case. Multicenter not only hospital-based studies evaluating observed knowledge and behaviors for current/recent cases were considered as being at low risk of bias and threat to

TABLE 1 | Examples of recommendations for the symptomatic management of febrile illnesses in children.

	Canada (18)	France (19)	Italy (20, 21)	UK (22)	USA (23)	WHO (24)
TEMPERATURE MEASUREMENT METHOD						
Rectal	Yes	Yes	No	No	Yes	Yes
Oral	Yes	Yes	No	No	Yes	Yes
Auricular	Yes	Yes	Yes	Yes	Yes	No
Axillary	Yes	Yes	Yes	Yes	Yes	Yes
FEVER DEFINITION						
≥38°C	Yes	Yes	*	Yes	Yes	Yes
WHEN TO START DRUG TREATMENT						
Based on a fever threshold	No	Yes	No	No		Yes
Based on symptoms	Yes	Yes	Yes	Yes	Yes	Yes
PHYSICAL TREATMENTS						
Adjust room temperature		Yes	No	No	Yes	Yes
Light clothing	Yes	Yes	No	Yes	Yes	Yes
Encourage fluid intake	Yes	Yes	No	Yes	Yes	Yes
Others			No		Sponging	
DRUG TREATMENT						
Monotherapy as first-line treatment	Yes	Yes	Yes	Yes		Yes
Acetaminophen	Yes	Yes	Yes	Yes	Yes	Yes
Ibuprofen	Yes	Yes	Yes	Yes	Yes	Yes
Acetylsalicylic acid	No	Yes	No	No	No	No

**Empty cases are not clearly addressed in recommendations.*

generalizability. Studies with one or more of the following characteristics were considered at high risk of bias and threat to generalizability: having a single center sample, being only hospital-based, or based on case scenarios.

Statistical Analyses

To describe "current" parents' knowledge and behaviors, we performed a fixed-effect meta-analysis by calculating an inverse-variance weighted mean frequency from studies performed during the last decade. Then, we tested for temporal changes in parents' knowledge and behaviors using inverse-variance weighted linear regression of frequency over time (in years). To describe those temporal changes, we reported mean frequencies of the first and last quinquennials over the study periods based on available data (the study periods may change across the different knowledge and behavior domains assessed).

Analyses were first performed using all included studies. Subsequently, we carried out a sensitivity analysis by restriction to studies with low risk of bias. For the sensitivity analysis, the number of studies was insufficient for calculating a mean frequency during the last decade and for analyzing temporal changes. Then, we compared parents' knowledge and behaviors during the last decade according to the economic development status of the country where the study was performed: countries with advanced economies (CAE) vs. countries with emerging and developing economies (CEE) (28). Lastly, we stratified the analyses of temporal trends according to the economic development status. All analyses were carried out using Stata v11 (StataCorp, College Station, Texas, USA).

RESULTS

Study Selection and Characteristics

The search identified 966 articles (**Figure 1**) that were screened for eligibility on titles and abstracts (n = 781) and full texts (n = 185). We identified 62 articles that met our inclusion criteria (Appendix 2 in **Supplementary Material**), corresponding to 64 primary studies published since 1980, reporting the knowledge and behaviors of 36,791 parents in 30 countries, including 47 studies (73%; n =2 6,138) performed in CAE, of which 14 (22%; n = 2,705) were from the USA (Appendixes 3–5 in **Supplementary Material**). The main parental attitudes and behaviors studied were temperature measurement methods (37/64; 58%), definition of fever (27/64; 42%), physical treatments (44/64; 69%), and drug treatments (41/64; 64%). The weighted mean age of pediatric participants, reported in 11/62 articles, was 22 months.

Risk of Bias of Included Studies

Thirty-one (48%) studies had single-center recruitment, 38 (59%) were hospital-based only, and 44 (69%) were based on theoretical knowledge and behaviors (case scenarios) (Appendixes 4, 5 in **Supplementary Material**). Five studies (8%; n = 12,334) were judged to be at low risk of bias (12, 29–32).

Parents' Knowledge and Behaviors

The weighted means of temperature measurement methods reported in studies conducted in the last decade were (**Table 2**): touching the child 42%, (95% confidence interval –CI–: 29–55%), and use of axillary 33% (95% CI: 12–54%), auricular 6% (95% CI:

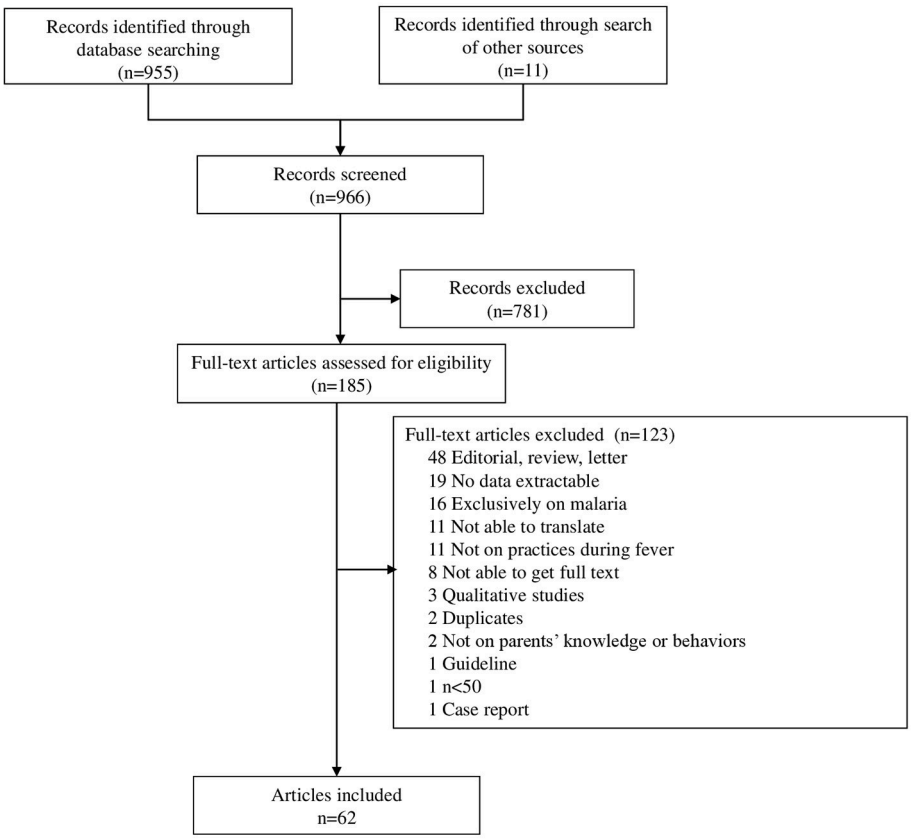

FIGURE 1 | Study flow diagram.

1–11%), rectal 5% (95% CI: 0–14%), and oral 1% (95% CI: 0–2%) thermometer. A statistically significant reduction over time was observed in the use of rectal measurement method (from 98% in the first quinquennial period to 4% in the last one; $p < 0.01$), with a corresponding increased use of axillary measurement (from 1 to 19%, $p < 0.01$).

The threshold commonly recommended for defining fever (i.e., 38°C) was known currently by 58% (95% CI: 52–64%) of parents (**Figure 2**, **Table 2**). We observed a statistically non-significant increase over time in the frequency of a definition of fever concordant with recommendations, from 38 to 55% ($p = 0.27$).

Common physical treatments used by parents were (**Table 2**): encouraging fluid intake (73%, 95% CI: 56–90%), light clothing (48%, 95% CI: 27–69%), sponging the child (36%, 95% CI: 19–53%), bathing (36%, 95% CI: 15–56%), and adjust room temperature (20%, 95% CI: 0–100%). A significant increase in encouraging fluid intake was observed over time (from 19 to 62%, $p = 0.01$).

Drug monotherapy was used by 67% (95% IC: 55–79%) of parents in studies conducted in the last decade (**Table 2**). The drugs used were: acetaminophen (87%, 95% CI: 78–96%), ibuprofen (28%, 95% CI: 15–40%), and acetylsalicylic acid (1%, 95% CI: 0–2%). A significant decrease was observed over time in the use of acetylsalicylic acid (from 60 to 1%, $p = 0.02$). No statistically significant changes were observed for acetaminophen (91 to 92%, $p = 0.09$) and ibuprofen (20 to 43%, $p = 0.72$).

Sensitivity Analysis for Studies With Low Risk of Bias

Only one study with low risk of bias was conducted during the last decade ($n = 6{,}596$) (12). The temperature measurement methods were axillary (6%), auricular (19%), rectal (64%), and oral (2%) thermometer. The recommended threshold used for defining fever was known by 61% of parents. Physical treatments used by parents were: encouraging fluid intake (78%), light clothing (62%), adjust room temperature (27%), bathing (20%), and sponging the child (17%). A drug monotherapy was used by 66% of parents: acetaminophen (78%), ibuprofen (29%), and acetylsalicylic acid (2%).

Stratified Analyses According to Countries' Economic Development

In CAE, we observed more frequent use of rectal measurement (57 vs. 1% in CAE and CEE, respectively, $p < 0.001$), oral measurement (2 vs. 0%, $p = 0.02$), auricular measurement (18 vs. 2%, $p < 0.001$), light clothing (64 vs. 35%, $p = 0.004$), and acetaminophen (92 vs. 71%, $p < 0.001$), but less frequent use of axillary measurement (8 vs. 85%, $p < 0.001$), sponging (24 vs. 66%, $p < 0.001$), and bathing (31 vs. 69%, $p = 0.001$).

TABLE 2 | Parents' knowledge and behaviors concerning febrile illnesses in children.

(%)	Countries with advanced economies				Countries with emerging and developing economies				All countries			
	Last decade[a]	1st quinquennial[b]	Last quinquennial[b]	P[c]	Last decade[a]	1st quinquennial[b]	Last quinquennial[b]	P[c]	Last decade[a]	1st quinquennial[b]	Last quinquennial[b]	P[c]
TEMPERATURE MEASUREMENT METHOD												
Rectal	57	98	53	<0.01	1	1	1	0.79	5	98	4	<0.01
Oral	2	1	2	0.39	0	0	0	0.35	1	1	1	0.96
Auricular	18	8	14	0.35	2	2	2	0.59	6	9	6	0.88
Axillar	8	1	10	0.17	85	91	85	0.10	33	1	19	<0.01
Touching	38	17	38	0.04	44	52	44	0.13	42	17	42	0.08
FEVER DEFINITION												
Temperature ≥38°C	60	46	60	0.37	54	30	54	0.32	58	38	55	0.27
PHYSICAL TREATMENTS												
Encourage fluid intake	72	19	34	0.03	79	79[d]	79[d]	0.92	73	19	62	0.01
Light clothing	64	19	63	0.03	35	21	35	0.61	48	19	47	0.17
Adjust room temperature	20	16	20	0.97	NA	NA	NA	NA	20	16	20	0.97
Bathe	31	32	28	0.46	69	36	69	0.02	36	32	34	0.25
Sponge	24	50	64	0.70	66	80	62	0.53	36	38	67	0.62
DRUG TREATMENTS												
Monotherapy	65	53	71	0.46	75	65	75	0.87	67	53	71	0.22
Acetaminophen	92	91	98	<0.01	71	83	71	0.03	87	91	92	0.09
Ibuprofen	32	20	41	0.87	23	13	24	0.09	28	20	43	0.72
AAS	1	60	1	0.07	2	4	2	0.09	1	60	1	0.02

[a]Inverse-variance-weighted pooled frequency in the last decade; [b]Inverse-variance-weighted pooled frequency of the first and last quinquennials with available data; [c]P-value of linear regression of inverse-variance-weighted frequencies over time (in years); [d]Same period of study; NA, No data available; AAS, acetylsalicylic acid.

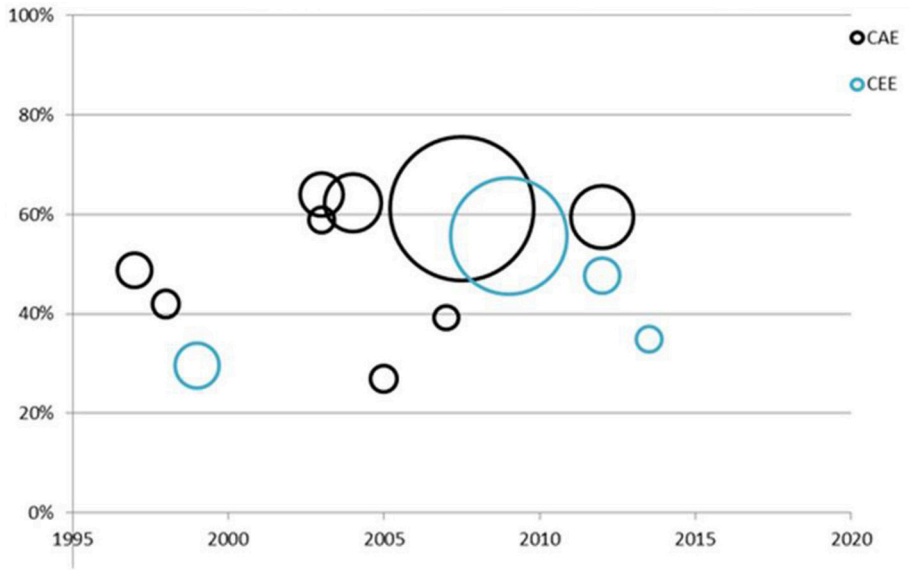

FIGURE 2 | Time trend of the frequency of parents citing 38°C as the threshold for the definition of fever in children. CAE, countries with advanced economies; CEE, countries with emerging and developing economies. Each point represents one study; dot size is proportional to inverse of the variance and thus the study weight in the regression.

In CAE, a significant increase over time was observed in the frequency of touching the child to measure fever (from 17 to 38%, $p = 0.04$), encouraging fluid intake (from 19 to 34%, $p = 0.03$), light clothing (from 19 to 63%, $p = 0.03$), and use of acetaminophen (from 91 to 98%, $p < 0.01$), along with a significant reduction in use of the rectal measurement (from 98 to 53%, $p < 0.01$). In contrast, studies performed in CEE showed a significant increase in bathing (from 36 to 69%, $p = 0.02$) and a significant reduction in use of acetaminophen (from 83 to 71%, $p = 0.03$).

DISCUSSION

Summary of Evidence

Published studies show an important and persistent gap between parents' knowledge and behaviors for the symptomatic management of febrile illnesses in children, on the one hand, and recommendations by health agencies and medical societies, on the other (2, 18, 23). "Fever phobia" seems to persist, with very frequent (>80%) use of antipyretic drugs, including in studies with low risk of bias and threat to generalizability, and both in countries with advanced and less advanced economies. The high frequency of antipyretic use could be justified if it aimed at making the child more comfortable, however most studies did not identify the goal of drug use, and in the few that reported it, 10–60% of parents reported using drugs to control the level of temperature rather than relieve discomfort (11, 15, 33–35). Frequent discordance between parents' knowledge and behaviors and recommendations were also observed for the measurement of temperature by touch (42% in studies performed during the last decade), a definition of fever different from 38°C (58%), and the use of bathing or sponging (36%). The data on temperature measurement by touch should be interpreted with caution, however, because the phrasing of the questions often did not allow distinguishing the exclusive use of touch and its use before confirmation by recommended methods. Important gains over time in the frequency of concordance with recommendations were reported for encouraging fluid intake (from 19–62%) and use of acetylsalicylic acid (from 60 to 1%).

We also observed differences between countries with advanced or less advanced economies. In CEE, we observed more frequent use of axillary temperature measurement (85% compared to 8% in CAE, respectively), bathing (69 vs. 31%), and sponging (66 vs. 24%) but less frequent use of drugs (acetaminophen: 71 vs. 92%; and ibuprofen 23 vs. 32%). These differences may be related to economic and cultural barriers and/or limited accessibility to current recommendations. Given the lack of detailed information on cultural background of population analyzed in included studies and ongoing recommendations in the region where they were performed, we were not able to formulate precise hypothesis that could explain these differences. However, it is well-known that the rectal route is not traditionally used for temperature measurement and drug administration in some countries, for cultural reason.

Implications for Clinical Practice and Public Health

Our study shows that effort is still required to de-dramatize fever among parents. Several reasons may explain the persisting gap between recommendations and parents' knowledge and behaviors, including insufficient evidence for recommendations and consequent discrepancies among them on key aspects of fever management, the low readability of patient educational tools, poor dissemination of guidelines (2), incorrect or suboptimal counseling and examples provided by healthcare providers (36), and resistance to change (such as positive

experiences with non-recommended practices based on older children). Health education interventions concerning fever in children may need to use alternative methods (such as mobile apps for smartphones and tablets, printed papers, advises during medical appointments, television spots, or e-campaigns) to reach parents and need to provide simple and clear guidance, especially for parents with a low educational level. The results of our systematic review and meta-analysis suggest that these renewed educational efforts should include knowledge as basic as the definition of fever (which was known by only 58% of parents −61% in CAE, 54% in CEE- in the last decade). The lack of international consensus on the threshold for defining fever is a barrier to the standardization of educational programs.

Implications for Research

One of the potential barriers to parents' uptake of educational messages is the lack of international consensus on some aspects of symptomatic management of febrile illnesses, including methods for measuring body temperature, the definition of child discomfort and clear indications for physical and drug treatments (2, 3, 18, 19, 21, 23, 24). For example (**Table 1**), some health agencies or scientific societies do not mention or discourage rectal temperature measurement, or the use of ibuprofen or rectal acetaminophen, while others still encourage them (2, 3, 20, 21, 24). This lack of consensus may reflect cultural differences in practices such as the use of the rectal route, genuine uncertainty in the case of acetaminophen or ibuprofen, or the fact that many recommendations appear pragmatic rather than evidence-based. A consensus on such areas would be helpful in reducing parental anxiety, which may actually be increased by differences in guidelines. As guidance is increasingly focused on the use of drugs to reduce discomfort, research on the dimensions of discomfort in the feverish child and tools to measure them would help operationalize these recommendations.

Only five studies (<10%) were at low risk of bias and only one of those was published in the last 10 years (12). As fever is a main source of drug consumption and consultation in children, future studies should try to minimize risk of bias and threats to generalizability by improving their designs.

Limitations

We arbitrarily excluded studies with <50 participants and those published before 1980. However, only one study was excluded because of insufficient number of participants (**Figure 1**), so this arbitrary choice probably had only a marginal influence on our results. We searched for publications only in MEDLINE, Google Scholar, and Science Citation Index and only those written in English, French, German, Italian, or Spanish. The strength and the direction of the bias related to these identification process and inclusion criteria are unclear.

Only five studies (<10%) had a low risk of bias (multicenter not only hospital-based studies evaluating observed attitudes for current/recent cases), only one of which dates from the last 10 years. Thus our findings may not be valid for current parents.

The use of linear regression to explore temporal changes in parents' knowledge and behaviors is arguable, as it may lack statistical power and tests only for linear trends. However, more classical meta-regression would have provided even lower statistical power to detect changes over time, given the limited number of available studies.

We were unable to restrict our analyses to younger children. Such a restriction may well modify parents' behaviors, owing to differences in practical issues (e.g., type of temperature measurement methods) or because fever phobia is more frequent among parents of very young children (37).

CONCLUSION

Despite significant changes over time, parents' knowledge and behaviors showed poor concordance with recommendations for the symptomatic management of febrile illnesses in their children. Our study identified main targets for future educational messages including basic ones such as definition of fever. This is likely to become more important over time as there is a general trend toward encouraging self-management of common conditions in infants and children by their families. Any educational message should avoid giving false reassurance about fever, as in a small number of cases it is an early symptom of more severe disease. Studies with low risk of bias that adequately evaluate current parents' knowledge and attitudes behaviors and an international consensus on basic recommendations are needed.

AUTHOR CONTRIBUTIONS

NBe conceptualized and designed the study, carried out the study selection, the data extraction, and the analyses, and drafted the manuscript. NH carried out the study selection, and the data extraction, and critically reviewed the manuscript. EC and EP conceptualized, designed the study, and critically reviewed the manuscript. NBi, EdB, AW, JS, MK, PL, SL, and SM critically reviewed the study protocol, participated in study identification, and critically reviewed the manuscript. JC critically reviewed the study protocol, statistical analyses, and drafted the manuscript. MC conceptualized and designed the study, and drafted the manuscript. All authors approved the final manuscript as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2018.00279/full#supplementary-material

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SYSTEMATIC REVIEW
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Antibiotic Use in Febrile Children Presenting to the Emergency Department: A Systematic Review

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Introduction: While fever is the main complaint among pediatric emergency services and high antibiotic prescription are observed, only a few studies have been published addressing this subject. Therefore this systematic review aims to summarize antibiotic prescriptions in febrile children at the ED and assess its determinants.

Methods: We extracted studies published from 2000 to 2017 on antibiotic use in febrile children at the ED from different databases. Author, year, and country of publishing, study design, inclusion criteria, primary outcome, age, and number of children included in the study was extracted. To compare the risk-of-bias all articles were assessed using the MINORS criteria. For the final quality assessment we additionally used the sample size and the primary outcome.

Results: We included 26 studies reporting on antibiotic prescription and 28 intervention studies on the effect on antibiotic prescription. In all 54 studies antibiotic prescriptions in the ED varied from 15 to 90.5%, pending on study populations and diagnosis. Respiratory tract infections were mostly studied. Pediatric emergency physicians prescribed significantly less antibiotics then general emergency physicians. Most frequent reported interventions to reduce antibiotics are delayed antibiotic prescription in acute otitis media, viral testing and guidelines.

Conclusion: Evidence on antibiotic prescriptions in children with fever presenting to the ED remains inconclusive. Delayed antibiotic prescription in acute otitis media and guidelines for fever and respiratory infections can effectively reduce antibiotic prescription in the ED. The large heterogeneity of type of studies and included populations limits strict conclusions, such a gap in knowledge on the determining factors that influence antibiotic prescription in febrile children presenting to the ED remains.

Keywords: pediatric emergency care, fever, children, antibiotic prescription, management

INTRODUCTION

Fever is the main complaint among pediatric emergency services (1). In only 15% (IQR 8·0–23·2%) a serious bacterial infection (SBI) is diagnosed with pneumonia and urinary tract infection (UTI) being the most prevalent (2, 3).

In contrast to the above, high antibiotic prescriptions are observed in febrile children (4, 5). Guidelines, or new diagnostic approaches have shown to effectively reduce antibiotic prescriptions in primary care (6–9). This is important because unnecessary antibiotic use increases antibiotic resistance (10, 11). In contrast to hospital based studies or primary care settings (11–15), few studies have been published in emergency department (ED) settings nor do we have valid estimates of potential benefits of antibiotic reducing interventions. Therefore our primary study aim is to assess antibiotic prescriptions for febrile children visiting the emergency department and their determinants. Secondary, we aim to investigate potential interventions that have been proven to be effective in the ED.

METHODS

Study Characteristics

All descriptive and interventional studies published in 2000–2017 reporting on antibiotic use in children (age under 18) with fever in the emergency department were eligible for this review.

Search Strategy

We searched Embase, Medline (OvidSP), Web-of-science, Scopus, Cinahl, Cochrane, PubMed publisher, and Google scholar for the (analogs of) keywords: fever, antibiotics, emergency department, children and antibiotic prescription. Initially search was performed in 2015 and updated in October 2017 (**Supplementary Material 1**). References were checked for additional articles to be included.

Inclusion

A screening by title/abstract resulted in potential eligible articles that underwent full text review. Two authors reviewed all articles; any discrepancies were solved by oral agreement between authors.

- Setting: Emergency department; if mixed settings, at least 30% (50 patients minimum) of the population needed to be admitted to the ED.
- Design: observational studies and randomized controlled trials with a minimum of 50 participants.
- Outcome: the studies had to report the number or percentage of antibiotics prescribed.
- Population: participants under the age of 18; if mixed ages, at least 20% of the population needed to be <18 years (with a minimum of 50) or age specific antibiotic prescriptions had to be presented. Studies on children with specific comorbidities only were excluded.
- Fever: at least 30% of all included children needed to have fever or the reason of visit was (reported) fever.

Quality Assessment of Included Articles

To compare the risk-of-bias of all these different study designs all articles were assessed using the MINORS criteria (16). Zero points were given for the item if not reported, one point if reported but insufficient and two points if reported and sufficient. As loss to follow-up was not applicable, due to emergency setting, we have let this particular item out of consideration; the maximum score for studies is 14 or 22 for respectively non-comparative and comparative studies. A maximum score on the MINORS criteria was needed to receive the status of a low risk of bias study (A) (17). For the final quality assessment we additionally used the sample size and the primary outcome. A high quality study was defined by status low risk of bias (A) on the MINORS, antibiotic prescription being the primary outcome and a sample size of at least 500 children. Two reviewers (EV and RO) have independently assessed all included studies. **Supplementary Material 2** contains the complete quality assessment.

Data Extraction and Analysis

Extracted data included: Author, year, and country of publishing, study design, inclusion criteria, primary outcome, median (or mean when median not available) age, number of included children. Aiming to invest determinants of antibiotic prescription, we additionally extracted (if available): diagnosis, type of antibiotics, type of physicians, and type of intervention.

Due to heterogeneity in participants, outcome measures, interventions and study designs, no statistical pooling but a qualitative analysis was performed (18). Results are presented for the 5 main diagnosis, i.e., fever, AOM, pneumonia, other respiratory tract infections (RTI other) and UTI, with a minimum of 50 cases per diagnostic group required.

RESULTS

Literature Search

We obtained 837 articles by literature search. Screening the full text articles excluded 97 out of 151, which leaves 52 articles for data extraction. Two additional studies were included by reference check of included studies (**Figure 1**).

Characteristics of the Included Studies

The study characteristics are presented in **Table 1** for the included 54 studies. Most studies come from the US ($n = 32$, 59%), 16 others came from Europe, and 6 others from Canada

Abbreviations: AB, antibiotic(s); AOM, acute otitis media; ARS, acute respiratory symptoms; ARTI, acute respiratory tract infection; BC, blood culture; CAP, community acquired pneumonia; CC, case control study; CI, confidence interval; CP, cohort study, prospective; CR, cohort study, retrospective; CS, cross sectional study; CSF, cerebrospinal fluid; d, days; ED, emergency department; EL, extreme leukocytosis; FWS, fever without source; GED, general emergency department; GEMP, general emergency medicine physician; ILI, influenza-like illness; ML, moderate leukocytosis; mo, months; NR, not reported; NS, not specified; PED, pediatric emergency department; PEMP, pediatric emergency medicine physician; qRCT, quasi-randomized controlled trial; RCT, randomized controlled trial; reg, registration; RIDT, rapid influenza diagnostic tests; RST, rapid streptococcal test; RVT, rapid viral testing; SBI, serious bacterial infection; SD, standard deviation; T, temperature; URTI, upper respiratory tract infection; UTI, urinary tract infection; y, years.

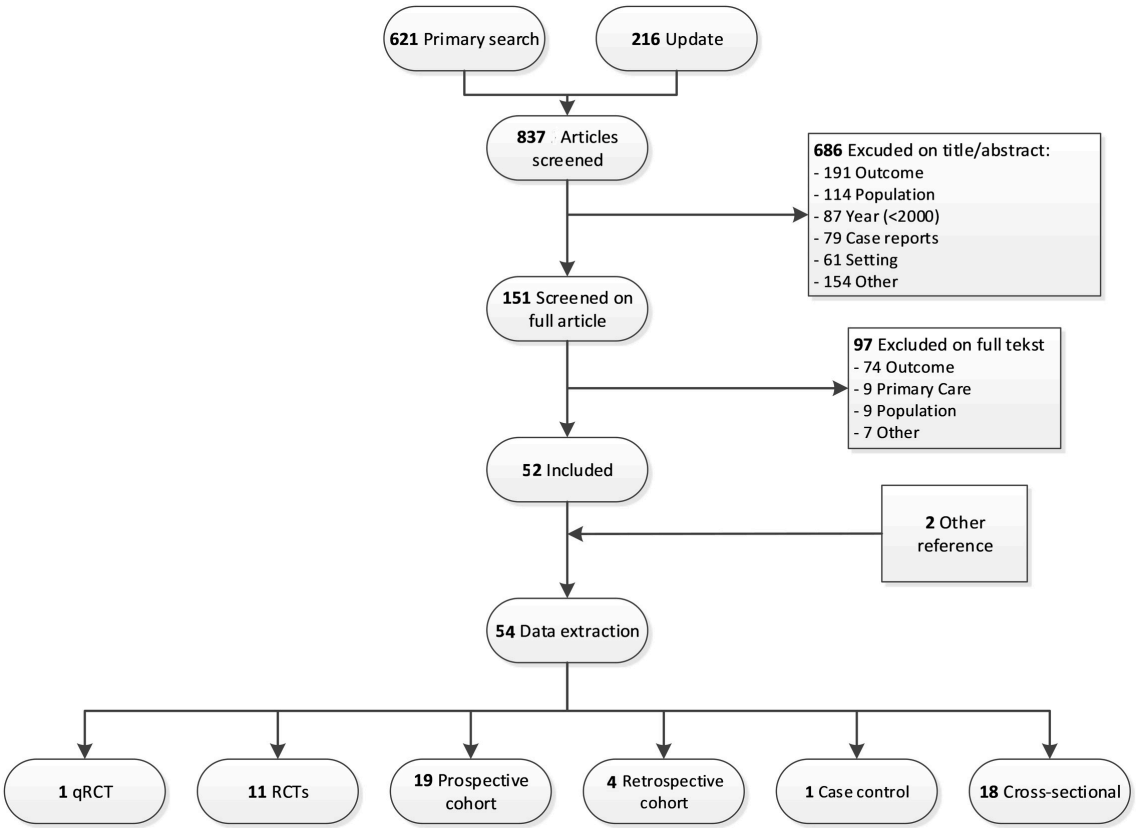

FIGURE 1 | Flowchart of the study selection and exclusion.

($n = 3$) (33, 36, 49), Australia ($n = 2$) (3), and Israel ($n = 1$) (26). The size of the studied population varied between 72 and 266.000 participants (median = 391). Most studies included children up to 36 months ($n = 14$, 25%) or all ages < 18 year ($n = 18$, 32%). Antibiotic prescription was the primary outcome in 33 studies (59%). Quality and feasibility assessment of the included studies (**Supplementary Material 2**).

Sixteen studies (29%) were considered as high quality and 17 (30%) were considered low quality. In general, observational studies did not describe sufficiently how sample size was approximated. Almost all high quality studies, except one (3), used antibiotic prescriptions as a primary outcome.

Antibiotic Prescriptions in Febrile Children and Specific Conditions

Table 2 presents the antibiotic prescriptions among the five diagnostic groups we distinguished. Sixteen out of 26 descriptive studies focused on febrile children in general, one paper specifically addressed acute otitis media (AOM) (30), two pneumonia (45, 63), four other respiratory infections (RTI other)(19, 23, 43, 57), and one urinary tract infections (UTI)(32). One paper on febrile children also provide separate numbers for pneumonia and UTI (3) and one for AOM (61). Two additional papers focused on respiratory infections and provided separate numbers for pneumonia, AOM and RTI other (44, 56).

Fever

Sixteen out of 26 studies focused on febrile children in general, seven of them selected children based on fever without source; five included febrile children based on additional testing (**Table 2**). In studies of general febrile populations only, antibiotic prescriptions ranged from 15 to 71% (3, 31, 35, 36, 39, 42, 50, 61, 71). The lowest prescriptions (15%) came from a study on parenteral empirical antibiotics only (50). Study quality did not influence antibiotic prescription rate.

Three high quality, six moderate quality and two low quality studies reported on SBI rate, which ranged from 7 to 41% (**Figure 2**) (3, 26, 35–38, 42, 44, 50, 60, 71). As the SBI rate in Khine et al. (42) is similar to antibiotic prescriptions, one may question how SBI is defined. Massin et al. (50) reports on parenteral antibiotics only and may not represent antibiotic prescription in total. Focusing on the remaining eight studies, we observe a trend toward higher antibiotic prescriptions with higher rates of SBI, although not significant.

In the studies on fever in general, we observed a higher prescriptions in children under the age of one (45 to 71%; weighted mean 58%), compared to older ones (prescriptions of 17 to 44%; weighted mean 28%), independent of study quality (**Figure 3**) (3, 28, 31, 35–37, 39, 42, 50, 71).

None of the studies on febrile children in general compared antibiotic prescriptions between countries. In the eleven studies

TABLE 1 | Characteristics of descriptive studies about antibiotic prescription.

Reference, Country	Study design	Age group/ inclusion	Median (IQR) or Mean age ± SD	Inclusion criteria	N children included	Quality
Ahmed et al. (19), US	CSp	0–18 years	NR	URTI	321	Low
Angoulvant et al. (20), France	CR	<18 years	17 months (7–40)	ARTI	53.055	High
Aronson et al. (21), US	CSr	29–56 days	46 days (37–53)	Fever	1626	High
			45 days (37–53)			
Ayanruoh et al. (22), US	CSr	3–18 years	NR	Clinical diagnosis of pharyngitis	8280	Low
Benin et al. (23), US	CSr	3–18 years	8.7 years (6–13)	Diagnosis pharyngitis	391	Moderate
Benito-Fernández et al. (24), Spain	CP	0–36 months	6.86 months ± 6.3°	Fever without source	206	Low
			6.55 months ± 6.8°			
Blaschke et al. (25) US◇	CSr	All ages	53% <18 years	Influenza	58	Low
Brauner et al. (26), Israel	CCr	3–36 months	NR	Fever and complete blood count	292	Moderate
Bonner et al. (27), US	RCT	2 months−21 years	NR	Influenza	202	Moderate
Bustinduy et al. (28), UK	CP	<16 years	2 years (1–4 years)	Fever or reported fever	1097	Moderate
Chao et al. (29), US	RCT	2–12 years	5.01 years (3.67–6.68)	AOM	206	Moderate
			3.73 years (2.82–5.75)			
Craig et al. (3), Australia	CP	<6 years	± 60% <24 months	Fever	15.781	High
Coco et al. (30), US	CSr	<12 years	± 2 years*	AOM	8325	High
Colvin et al. (31), US	CP	2–36 months	8.0 months	Fever without source ¥	75	Low
Copp et al. (32), US	CSr	<18 years	±6 years*	UTI	1828 (36% in ED)	Low
Doan et al. (33), Canada	RCT	3–36 months	15 months (3–36)	Acue respiratory symptoms	199	Moderate
			14 months (4–34)			
Fischer et al. (34), US	CP	2–18 years	68% 2–6 years	AOM	144	Low
Galetto Lacour et al. (35), Switzerland	CP	7 days −36 months	11 months*	Fever without source ¥	124	Moderate
Galetto-Lacour et al. (35), Switzerland	CP	7 days −36 months	7.2 months (0.4–31.1)	Fever without source ¥	99	Low
			9.7 months (0.7–34)			
Goldman et al. (36), Canada	CP	<3 months	48.7 days ± 23.6°	Fever	257	Low
Houten et al. (37), Netherlands	CP	2–60 months	21 months ± 16°	Fever and LRTI symptoms or without source	577	Moderate
Irwin et al. (38), UK	CP	<16 years	2.4 years (0.9–5.7)	Fever and blood tests	1101	High
Isaacman et al. (39), US	CR	3–36 months	18 months ± 9.8°	Fever without source in a GED¥	79	Low
			16.3 months ±8.8°	Fever without source in a PED¥	498	
Iyer et al. (40), US	RCT	2–24 months	±75% 6–24 months	Fever	700	Moderate
Jain et al. (41), US	CP	<18 years	NR	Fever	19075	High
Khine et al. (42), US	CR	3–36 months	15.2 months ±8.7°	Reported fever in GED	237	Moderate
		3–36 months	16.6 months ±9.1°	Reported fever in PED	224	
Kilic et al. (43) Turkey	CSr	3–140 months	41.2 months ±31°	Asthma, croup, Bronchiolitis	2544	Low
Kornblith et al. (44), US	CSr	0–18 years	± 56% 1–5 years	ARTI	6461	High
Kronman et al. (45), US	CSr	1–18 years	50–60% 1–5 years	CAP	266.000	High
Lacroix et al. (46), France	RCT	7 days−36 months	3.4 months (1.5–10.4)	Fever without source	271	High
			4.8 months (1.7–10.4)			

(Continued)

TABLE 1 | Continued

Reference, Country	Study design	Age group/ inclusion	Median (IQR) or Mean age ± SD	Inclusion criteria	N children included	Quality
Linder et al. (47), US	CSr	3–17 years	45% 6–11 years	Sore throat	6955	High
Li-Kim-Moy et al. (48), Australia	CR	0 ≤ 18 years	3.1 years (1.1–7.4)	Lab proven influenza	301	Moderate
Manzano et al. (49), Canada	RCT	1–36 months	12 ± 8 months°	Fever	384	High
			12 ± 8 months°			
Massin et al. (50) Belgium	CP	1–36 months	13.8 months ±9.7°	Fever without source ¥	376	Moderate
McCaig et al. (51), US	CSr	3 months−2 years	NR	Fever and BC (discharged)	5.4% of all ED visits	Low
McCormick et al. (52), US	RCT	6–72 months	±60% <1 years	AOM	209	Moderate
Murray et al. (53), US	CP	<56 days	36 days ± 13.8	Fever	520	Low
Nelson et al. (54), US*	CP	3 months−18 years	2.8 years (4.4)	Pneumonia	3220	High
Nibhanipudi et al. (55), US*	CP	2–17 years	5.72 years ± 0.38° (m)	AOM	100	Low
			7.41 years ± 0.75° (f)			
Ochoa et al. (56), Spain	CSr	0–18 years	±3 years (1 months−18 years)	ARTI	6249	High
Ong et al. (57), US	CP	All ages (20% child)	33 years	URTI	272	Moderate
Özkaya et al. (58), Turkey	CSp	3–14 years	5.7 years ± 3.4°	Influenza like illness	97	Low
			4.25 years ± 2.02			
Ouldali et al. (59), France	qRCT	<18 years	1.6 years (0.7–3.6)	ARTI	196.062	High
			1.7 years (0.7–3.7)			
Planas et al. (60), Spain	CP	<3 months	35 days ± 31°	Fever without source and BC (admitted) ¥	381	Moderate
Ploin et al. (61), France	CP	<36 months	NR	Fever during influenza season	538	Moderate
Poehling et al. (62), US	RCT	<5 years	NR	Fever or ARS during influenza season	305	Moderate
Shah et al. (63), US	CSr	1–18 years	± 63% 1–4 years	Fever and cough or respiratory distress	3466	Moderate
Sharma et al. (64), US	CSr	2–24 months	9 months °	Fever and positive influenza test	72	Low
Spiro et al. (65), US	RCT	6–35 months	17.3 months°	Fever or ARS	681	High
			17.2 months°			
Spiro et al. (66), US	RCT	6 months−12 years	3.2 years	AOM	283	High
			3.6 years			
Trautner et al. (67), US	CSp	<18 years	17 months (11–25 months)	Hyperpyrexia	103	Moderate
de Vos-Kerkhof et al. (68), Netherlands	RCT	1 months−16 years	1.7 years (0.8–3.9)	Fever	439	Moderate
			2.0 years (1.0–4.2)			
Waddle and Jhaveri, (69), US	CSr	3–36 months	17 months ± 11°	FWS and BC	423	Low
			15 months ± 10°			
Wheeler et al. (70), US	CP	≤18 years	3 years (1 months−20 years)	Viral infections	144	Moderate

CC, case control; CP, prospective cohort; CR, retrospective cohort; CS, cross-sectional; r, retrospective; p, prospective.
**Estimated/calculated from numbers in article. °Mean age is given, median age was not reported. ¥ Fever without source: as defined in corresponding study.*

TABLE 2 | Antibiotic prescription per diagnosis.

Reference, Country	Age group/ inclusion	Median (IQR) or Mean age ± SD	Inclusion criteria	N children included	N antibiotics, % of study population[ǂ]
FEVER IN GENERAL					
Bustinduy et al. (28), UK	<16 years	2 years (1–4 years)	Fever or reported fever	1097	44%
Colvin et al. (31), US	2–36 months	8.0 months	Fever without source ¥	75	45%
Craig et al. (3), Australia	<6 years	± 60% <24 months	Fever	15.781	27%
Galetto Lacour et al. (35), Switzerland	7 days−36 months	11 months*	Fever without source ¥	124	62.1%
Galetto-Lacour et al. (35), Switzerland	7 days−36 months	7.2 months (0.4–31.1) 9.7 months (0.7–34)	Fever without source ¥	99	71%
Goldman et al. (36), Canada	<3 months	48.7 days ± 23.6°	Fever	257	55%
Houten et al. (60), Netherlands	2–60 months	21 months ± 16°	Fever and LRTI symptoms or without source	577	39%
Isaacman et al. (39), US	3–36 months	18 months ± 9.8°	Fever without source in a GED¥	79	39.2%
		16.3 months ±8.8°	Fever without source in a PED¥	498	16.7%
Khine et al. (42), US	3–36 months	15.2 months ±8.7°	Reported fever in GED	237	41%
	3–36 months	16.6 months ±9.1°	Reported fever in PED	224	27%
Massin et al. (50), Belgium	1–36 months	13.8 months ± 9.7°	Fever without source ¥	376	15%
Ploin et al. (61), France	<36 months	NR	Fever during influenza season	538	34.8%
FEVER AND SELECTION ON ADDITIONAL TESTING OR CHARACTERISTICS					
Irwin et al. (38), UK	<16 years	2.4 years (0.9–5.7)	Fever and blood tests	1101	855, 78%
Trautner et al. (67), US	<18 years	17 months (11–25 months)	Hyperpyrexia	103	46, 61.3%
Brauner et al. (26), Israel	3–36 months	NR	Fever and complete blood count	292	148, 50.7%
Planas et al. (60), Spain	<3 months	35 days ± 31°	Fever without source and BC (admitted) ¥	381	281, 73.8*%
AOM					
Coco et al. (30), US	<12 years	± 2 years*	AOM	8325	82.6%
Kornblith et al. (44), US	0–18 years	± 56% 1–5 years	AOM	647	88%
Ochoa et al. (56), Spain	0–18 years	±3 years (1 months−18 years)	AOM	821	93%
Ploin et al. (61), France	<36 months	NR	Fever during influenza season	18	89%
PNEUMONIA					
Craig et al. (3) Australia	<6 years	± 60% <24 months	Pneumonia	533	69%
Kornblith et al. (44), US	0–18 years	± 56% 1–5 years	Pneumonia	657	86%
Kronman et al. (45), US	1–18 years	50–60% 1–5 years	CAP	266.000	86.1%
Ochoa et al. (56), Spain	0–18 years	±3 years (1 months−18 years)	Pneumonia	288	93%
Shah et al. (63), US	1–18 years	± 63% 1–4 years	Pneumonia	347	82%
RTI OTHER					
Ahmed et al. (19), US	0–18 years	NR	URTI	321	43%
Benin et al. (23), US	3–18 years	8.7 years (6–13)	Diagnosis pharyngitis	391	23%
Kilic et al. (43), Turkey	3–140 months	41.2 months ±31°	Asthma, croup, Bronchiolitis	2544	16.6%
Kornblith et al. (44), US	0–18 years	± 56% 1–5 years	URTI	5157	36%
Ochoa et al. (56), Spain	0–18 years	±3 years (1 months−18 years)	URTI	5140	51%
Ong et al. (57), US	All ages (20% child)	33 years	URTI	272	83, 31%
UTI					
Copp et al. (32), US	<18 years	±6 years*	UTI	1828	70%
Craig et al. (3), Australia	<6 years	± 60% <24 months	Fever	543	66%

**Estimated/calculated from numbers in article.*

°Mean age is given, median age was not reported.

¥ Fever without source: as defined in corresponding study.

ǂ Antibiotic prescription is given for reported age group, except for Ong et al (57) antibiotic use for all ages is given.

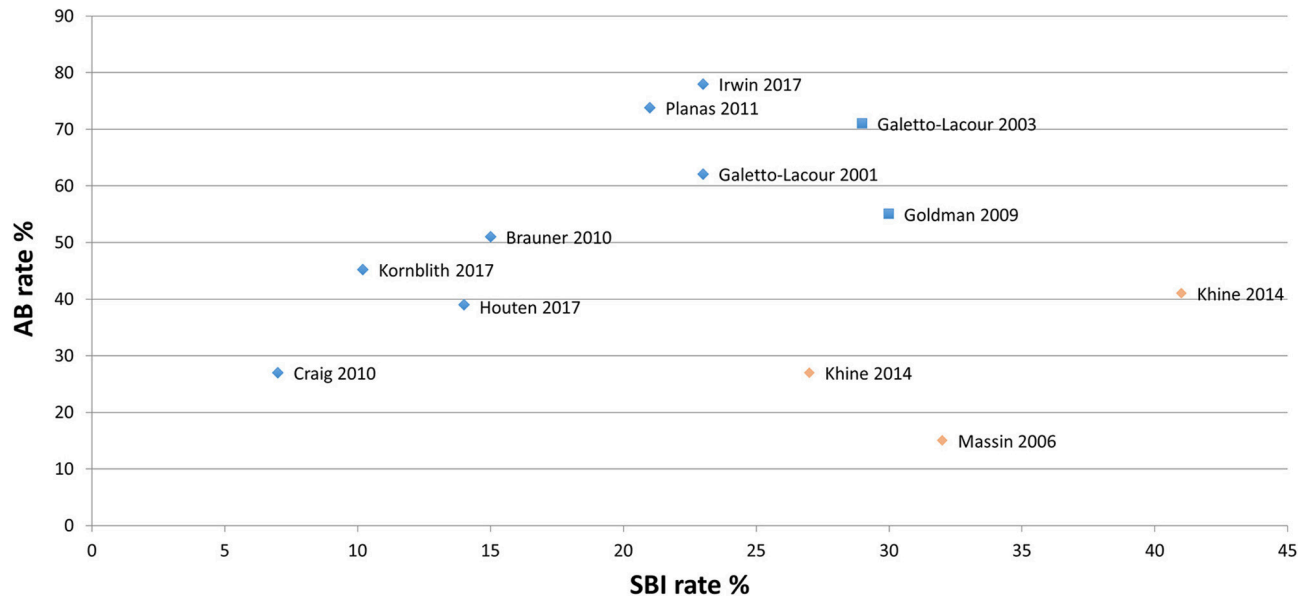

FIGURE 2 | Serious bacterial infection rate and antibiotic prescriptions per study. *High/Moderate quality*, *High/Moderate quality, outlier*, *Low quality*, *Low quality, outlie*.

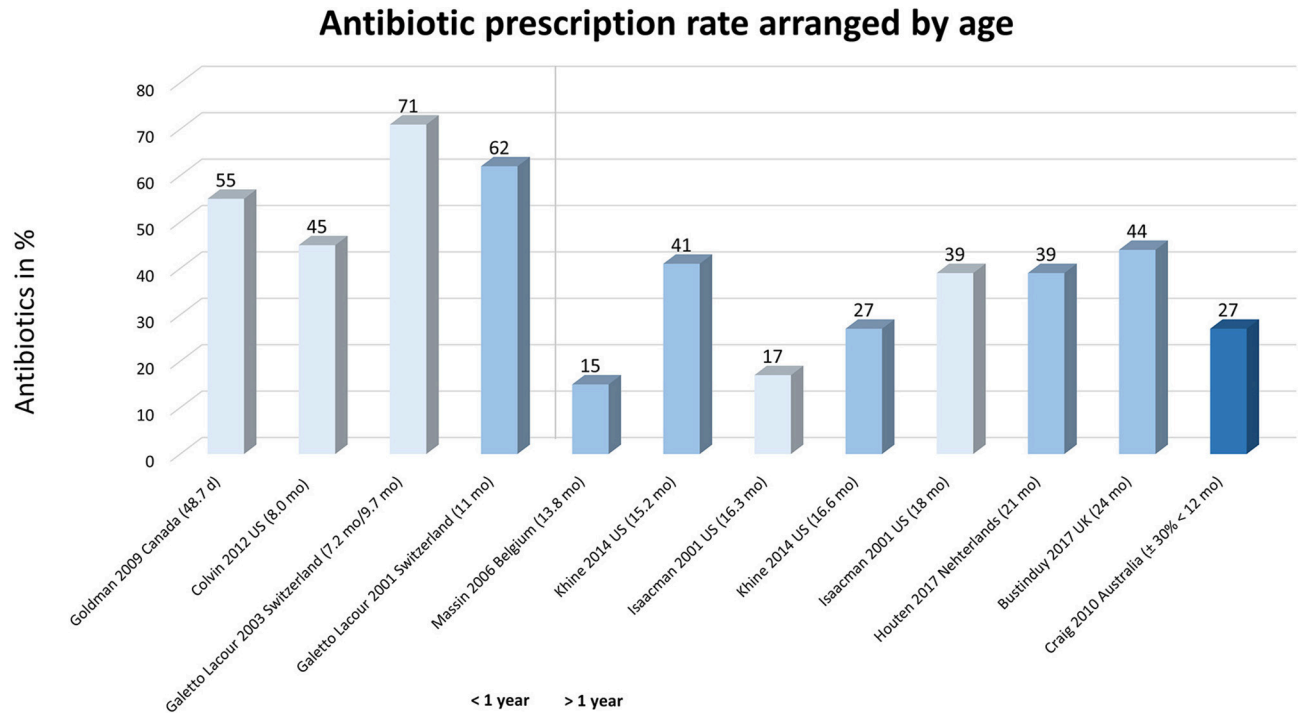

FIGURE 3 | Antibiotic prescriptions arranged on age in children with fever. Studies are arranged by age, i.e., left represents younger children to right (older ages). Light bars represent studies with a low quality.

(3, 28, 31, 35–37, 39, 42, 50, 61, 71) on children with fever in general (without additional testing), the highest prescriptions were reported in a Swiss study (71%) (35) and the lowest in a study originating from the US (17%) (39). The three studies originating from the US reported antibiotic prescription between 39–45% (31, 39, 42); for the two Swiss studies this varied

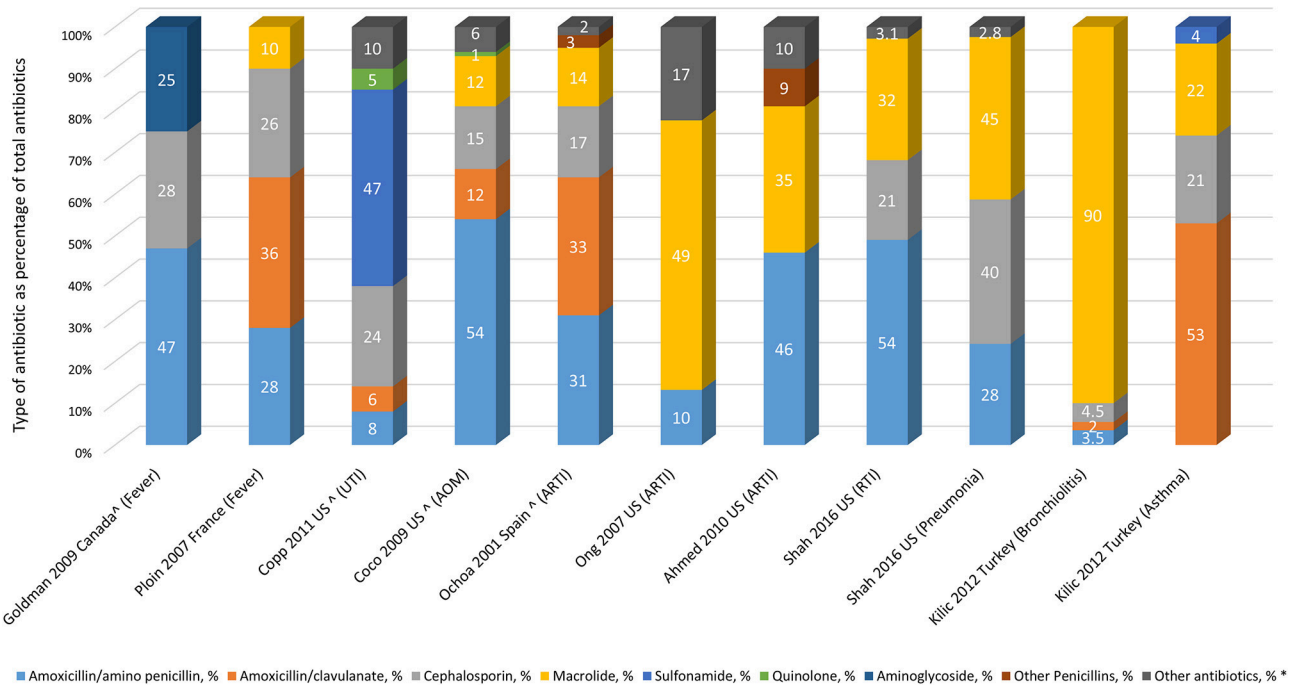

FIGURE 4 | Type of antibiotic as percentage of total antibiotics prescribed per study. *As defined in article. Ahmed et al. (19): not specified; Copp et al. (32): nitrofurantoin and others are not specified antibiotics. Coco et al. (30): not specified. Ochoa et al. (56): trimethoprim/sulfamethoxazole, clindamycin, fosfomycin, rifampin, trimethoprim, topical use and others are not specified. Ong et al. (57): trimethoprim/sulfamethoxazole; Shah et al. (63): not specified. ^Calculated from article as percentage of total antibiotics, in article given as percentage of cases.

from 62 to 71%, although originating from the same hospital (35, 71).

Antibiotic Prescription for Specific Diagnoses

Four studies provided data for antibiotic prescription in AOM, ranging from 88–93%. We could not determine influences of age on prescriptions. Five studies reported on antibiotic prescription in pneumonia, ranging from 69 to 93%. The study with the lowest prescription (3) included children <6 years only compared to the other four (including children in the range of 1-18 years). Antibiotic prescription in RTI other (6 studies) varied on a broader range from 17 to 51%, but could not be related to age. Only two studies provided information on antibiotic prescription in UTI, ranging from 66 to 70%.

Type of Antibiotic Prescription

Nine out of 26 (35%) studies [two high quality (30, 56)] reported on antibiotic type (**Figure 4**). Six studies addressed respiratory tract infections (19, 30, 43, 56, 57, 63) and five were conducted in the US (19, 30, 32, 57, 63). We did not observe a predominance for one antibiotic type for a specific diagnosis or country; amoxicillin was always reported. Studies describing cephalosporin use ($n = 7$) included both second or third generations.

Prescribing Physician

Five (39, 42, 47, 63, 72) out of seven studies [three high quality studies (44, 47, 66)], reported significant lower antibiotic prescriptions by pediatric emergency physicians compared to general emergency physicians (**Table 3**). Two addressed young children with fever without source (39, 42), and five addressed older children with respiratory tract infections (19, 44, 47, 63, 65).

The Effect of Interventions on Antibiotic Prescription

Nine out of 27 studies on interventions for antibiotic prescription (32%) reported about rapid viral testing (22, 24, 25, 27, 33, 40, 58, 62, 64), four about delayed antibiotic prescription in acute otitis media (29, 34, 52, 66), six about guideline/management strategies (20, 21, 41, 53, 59, 68), four about laboratory tests (22, 46, 47, 49) and five using other interventions (**Table 4**). In fourteen studies (50%) a significant reduction in antibiotic use was found.

Interventions for AOM

Interventions with a significant effect on antibiotic reduction were guidelines and the wait-and-see prescription in acute otitis media (AOM). For this latter a significant reduction was found in four articles (three of them with moderate to high quality) (29, 34, 52, 66).

TABLE 3 | Difference in antibiotic prescription between general physicians and pediatric physicians.

Reference, Country	N Antibiotics given by GEMP/N seen by GEMP % antibiotics	N antibiotics given by PEMP/N seen by PEMP % antibiotics	Inclusion criteria
Isaacman et al. (39), US	37/79, 39%	83/498, 17%	FWS
Khine et al. (42), US	97/237, 41%	61/224, 27%	FWS
Ahmed et al. (19), US	NR/238, 32%	NR/345, 17%	URTI
Kornblith et al. (44), US	NR, 46%	NR, 42%	ARTI
Shah et al. (63), US	2946, 50%	520, 35%	Febrile RTI
Linder et al. (47), US	NR, 60%	NR, 47%	Sore throat
Spiro et al. (65), US*	NR, 30%	NR, 26%	Fever/ARS

*No significant statistical difference was found.
High quality study.
Moderate quality study.
Low quality study.

Viral Testing Intervention

Most studies on interventions for reduction of antibiotic prescription addressed rapid viral testing for influenza (RVT, $n = 9$). Fewer antibiotics were prescribed when the RVT is positive (24, 25, 27, 64), although not confirmed by studies on the impact of RVT use vs. not using RVT in the ED (27, 40, 58, 62). Only one low quality study reported a significant difference for this topic (58). The use of point-of-care testing above testing on indication had only significant benefit in children with proven influenza (33, 48). One study reported reduced length of stay, but no effect on antibiotic prescription (48).

Other Interventions

Three high quality studies showed a significant reduction in antibiotic prescription by a guideline for lower respiratory infections or infants with fever (20, 21, 41). Among two articles on streptococcal A testing, the article with the highest quality didn't find a significant reduction (22, 47). Introduction of a clinical pathway for young febrile infants showed reduced time to first antibiotic dose, but did not evaluate the effect on antibiotic prescription itself (53). The use of chest radiographs in particular reduces antibiotics in children with low clinical suspicion of pneumonia (54). For all other interventions no significant reduction was found on antibiotic prescription (46, 49, 65, 69, 70).

DISCUSSION

Interpretation of Main Findings

We observed a highly variable reported antibiotic prescriptions in children presenting to a general or pediatric ED in the five major groups of diagnosis. Studies on a specific diagnosis, such as AOM, pneumonia, or UTI report higher antibiotic prescriptions. However, studies are too heterogeneous to study true effects of determinants. Strong evidence was found for watchful waiting in AOM and implementation of guidelines for fever or respiratory infections to reduce antibiotic use in the ED. Intervention studies report mostly on rapid viral testing for influenzae (RVT) to reduce antibiotic prescription, but its effect is controversial.

It is important to note that the high variability in antibiotic prescription observed in our systematic review differ from reported antibiotic prescriptions from literature, or websites (12, 73). However, these numbers are based on national or local registries and include in-hospital patients, not reflecting our interest on use of antibiotics in ED settings. Next, not all countries are represented in our systematic review and only Switzerland, USA are represented by more than one study. For the latter two, however we observed high variability in antibiotic prescription within studies of the same country. Even within studies focusing on similar group of diagnoses, we observed a large heterogeneity in their way of patient selection and their type of febrile illness. Therefore, we think these antibiotic prescriptions cannot be considered to be representative for the general population of febrile children in a country.

Limited evidence was found for age effects on antibiotic prescriptions, potentially due to age distribution among study populations. Infants below 2 months are underrepresented in our review. From community studies, we know that pre-school children are more frequently exposed to antibiotic therapy (13).

After exclusion of two outlier studies given their patient selection and outcome definition (42, 50), we observed in studies on children with fever a trend toward higher antibiotic prescriptions in studies with higher SBI rates is noticeable. This, however, only explains some variation in antibiotic prescription.

Similar to studies in primary care, watchful waiting intervention seems highly effective for reducing antibiotic use in AOM at the ED (74). Results however are limited to patients above the age of 6 months that did not appear toxic and it is questionable if the study populations were large enough to detect serious adverse outcomes such as meningitis. Although the most frequently studied intervention, rapid viral testing for influenza has no additional effect above testing on indication and controversial evidence was found for its effect. Effects of guidelines are seen in two well-defined groups (respiratory infections or young febrile infants) and including a well-defined implementation plan. Implementation of a clinical decision model to reduce antibiotic prescriptions was only tested in a tertiary pediatric university ED and antibiotic reduction was not a primary outcome of this study (17). All other interventions are not (yet) proven to be effective for reducing the antibiotic prescriptions in children on the ED. Overall the evidence to reduce antibiotic prescription in the emergency department remains limited. We observed a general association between antibiotic prescription and the type of prescriber, i.e., pediatricians prescribe less antibiotics than general physicians may suggest that guideline implementation could be most effective in hospitals with general physicians treating children in the ED.

Limitations

The quality of the studies that reported about fever in general was low to moderate, with only one high quality study (3). Specific drawbacks of study design are included in the MINOR

TABLE 4 | Influence of intervention on antibiotic prescription.

Reference, Country	Median (IQR) or Mean age ± SD ¥	Intervention	Inclusion	N intervention total, % AB	N controls total, % AB
FEVER IN GENERAL					
Aronson et al. (21), US	46 days (37–53)	CPG recommending ceftriaxone compared to no CPG	Fever	306, 64.1%ˆ	1.304, 11.7%ˆ
	45 days (37–53)				
		CPG recommending against ceftriaxone compared to no CPG		313, 10.9%ˆ	1.304, 11.7%ˆ
Jain et al. (41), US	NR	Physician feedback through scorecards	Fever	8.961, 10.8%	1.0114, 12%
Lacroix et al. (46), France	3.4 months (1.5–10.4)	Lab Score	FWS	131, 41.2%	140, 42.1%
	4.8 months (1.7–10.4)				
Manzano et al. (49), Canada	12 ± 8 months°	PCT testing	Fever	192, 25%	192, 28%
	12 ± 8 months°				
Murray et al. (53), US	36 days ± 13.8	Implementation of a clinical pathway	Fever	296, 69%	224, 72%
de Vos-Kerkhof et al. (68), Netherlands	1.7 years (0.8–3.9)	Clinical decision model	Fever	219, 35.6%	220, 41.8%
	2.0 years (1.0–4.2)				
(SUSPICION OF) BACTERIAL INFECTIONS					
Nelson et al. (54), US *	2.8 years (4.4)	Antibiotic prescription rate before and after CXR result	Pneumonia	1610, 23%	1610, 7%
de Vos-Kerkhof et al. (68), Netherlands	1.8 (0.9–4.1)	Clinical decision model	Fever and SBI	192, 22.9%	192, 27.1%
Waddle and Jhaveri (69), US	17 months ± 11°	PCV7	FWS and BC	275, 57.2%	148, 60.8%
	15 months ± 10°				
INFLUENZA					
Blaschke 2014 (25), US◇	53% < 18 years	Rapid viral testing (positive/negative RVT)	RVT performed	NR, 11%	NR, 47%
Benito-Fernández et al. (24), Spain	6.86 months ± 6.3°	Rapid viral testing (positive/negative RVT)	Fever without source	84, 0%	122, 38.5%
	6.55 months ± 6.8°				
Bonner et al. (27), US	NR	Rapid viral testing (RVT /no RVT)	Influenza positive	96, 7%	106, 25%
Doan et al. (33), Canada	15 months (3–36)	Rapid viral testing (POCT/standard testing)	Acute respiratory symptoms	89, 18%	110, 21%
	14 months (4–34)				
Iyer et al. (40), US	±75% 6–24 months	Rapid viral testing (RVT/ no RVT)	Fever	345, 25.3%	355, 30.5%
Li-Kim-Moy et al. (48), Australia	3.1 years (1.1–7.4)	Rapid viral testing (POCT/standard testing)	Lab proven influenza	236, 33%	65, 54%
Özkaya et al. (58), Turkey	5.7 years ± 3.4°	Rapid viral testing (RVT /no RVT)	Influenza-like illness	50, 58%	47, 100%
	4.25 years ± 2.02°				
Poehling et al. (62), US	NR	Rapid viral testing (RVT/no RVT)	Fever or ARS during influenza season	135, 32%	170, 29%
Sharma et al. (64), US	9 months°	Rapid viral testing (RVT /no RVT)	Fever and positive influenza test	47, 2%	25, 24%
AOM					
Chao et al. (29), US	5.01 years (3.67–6.68)	Delayed prescription with and without prescription	AOM	100, 19%	106, 46%
	3.73 years (2.82–5.75)				
Fischer et al. (34), US	68% 2–6 years	Wait-and-see prescription in AOM	AOM	144, 27%	N.A.

(Continued)

TABLE 4 | Continued

Reference, Country	Median (IQR) or Mean age ± SD ¥	Intervention	Inclusion	N intervention total, % AB	N controls total, % AB
McCormick et al. (52), US	±60% < 1 years	Wait-and-see prescription in AOM	AOM	100, 34%	109, 100%
Nibhanipudi et al. (55), US*	5.72 years ± 0.38° (m) 7.41 years ± 0.75° (f)	WBC >15.000 or WBC <15.000	AOM	93, 3%	7, 100%
Spiro et al. (66), US	3.2 years 3.6 years	Wait-and-see prescription in AOM	AOM	138, 38%	145, 87%
RTI Other					
Angoulvant et al. (20), France	17 months (7–40)	Implementing guidelines	ARTI	NR, 21%	NR, 32.1%
Ayanruoh et al. (22), US	NR	Rapid streptococcal testing	Clinical diagnosis of pharyngitis	6.557, 22.45%	1.723, 41.38%
Linder et al. (47), US	45% 6–11 years	GABHS testing in sore throat	Sore throat	NR, 48%	NR, 51%
Ouldali et al. (59), France	1.6 years (0.7–3.6) 1.7 years (0.7–3.7)	Implementation of national guidelines	ARTI	134.450,−28.4%	61.612
Spiro et al. (65), US	17.3 months° 17.2 months°	Tympanometry for reduction antibiotics in AOM	Fever or ARS	341, 28.8%	340, 26.8%
Wheeler et al. (70), US	3 years (1 months−20 years)	Videotape in waiting room	Viral infections	71, 4.2%	73, 6.8%

^*Only parenteral antibiotic prescription rate is given. Highlighted studies indicate studies with significant results.*
**Estimated/calculated from numbers in article.*
°*Mean age given, median age not reported.*

assessment as a measure of quality. The use of MINORS in combination with the study population and study aim helps to increase the reproducibility of this review and made it possible to compare the different levels of evidence (16). Most studies did not reported on missing values regarding antibiotic prescription, which could lead to an underestimation of antibiotic prescriptions. In a substantial part of the included papers, antibiotic prescription was not the primary outcome. This may explain some diversity in antibiotic prescriptions, although this was partially corrected for in the quality assessment.

This systematic review focuses on prescription of antibiotics in the ED setting. In many European countries, antibiotics are available as over the counter drugs as well (75). This issue is not accounted for by any of the articles, which may lead to a general underestimation of the antibiotic use.

Unfortunately, we observed a large heterogeneity of the studies or had only 1 study per diagnosis group, hampering meta-analysis. Most heterogeneity is caused by specific patient selection (age, setting), by study design (intervention vs. observational cohort study). This also applies to the population of febrile children <36 months that constitute the majority of ED attendances.

Future Research Recommendations

To validly estimate baseline antibiotic prescriptions in children with fever presenting to the emergency department we need observational studies including the general spectrum of febrile children. Being able to determine influences of antibiotic prescription, we should address geographical and cultural influences, differences in setting, adherence area, general patient characteristics, and descriptors of illness severity. Insight in these determinants may help to define targets for intervention to reduce antibiotic prescriptions. Next, this information will contribute to valid power calculations for intervention studies and to generalize effects to other settings.

CONCLUSION

A summary of studies on antibiotic prescription in the 5 main diagnostic groups at the ED did not yield uniform outcomes. There seems to be a trend toward higher antibiotic prescriptions in younger children and for diagnoses that are more often related to bacterial infections. Delayed antibiotic prescription in children with acute otitis media and guidelines for fever/LRTI seem useful to reduce antibiotic prescriptions at the ED. However no strict conclusions can be drawn on the basis of this review because of the large heterogeneity of type of studies and included populations. This means that there is still a gap in knowledge on the determining factors that influence antibiotic prescription in febrile children presenting to the ED. A multicentre study including a wide range of countries on a general population of febrile children would be recommended to provide a valid baseline of antibiotic prescriptions in

general, and influencing factors that identify targets for future interventions.

AUTHOR CONTRIBUTIONS

EvdV was responsible for search, dataextraction and writing of the manuscript. HM, SM, and AG contributed to datainterpretation and writing of the manuscript. RO concepted the idea of the paper, supervised search, dataextraction, and writing of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2018.00260/full#supplementary-material

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Contemporary Trainee Knowledge of Autism: How Prepared Are Our Future Providers?

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Background: Over the last several decades, the prevalence of Autism Spectrum Disorder (ASD) has continued to increase, creating a unique challenge for general physicians who are likely to encounter these patients in their practice. The primary aim of this cross-sectional study design was to identify potential knowledge gaps that were present among medical students and pediatric trainees (interns, residents, and fellows) particularly during the management of a sick child with ASD.

Methods: A 23-question online survey was developed and distributed to medical students and pediatric trainees at a tertiary children's hospital affiliated with a medical school.

Results: Medical students and pediatric trainees reported a low general knowledge of ASD and were unfamiliar with sensory issues that are often present in these children. Increased discomfort and insufficient didactic and clinical training for providing care to children with ASD during an acute illness were also identified. Both medical students and trainees reported the need for increased education and training, preferentially via patient interaction and small group-based learning. We found that as education/training levels increased, participants perceived increased comfort, and knowledge in managing an ill child with ASD.

Conclusions: A perceived knowledge gap and discomfort is present amongst medical students and pediatric trainees on the management of children with ASD. Across all education levels, awareness for sensory dysregulation in ASD children is low. Education programs using direct patient interaction and small group learning were the preferred training modalities to learn how to provide optimal care for children with ASD.

Keywords: autism, sensory dysregulation, sensory processing disorder, medical education, ASD, communication, pediatric

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BACKGROUND

The prevalence for Autism Spectrum Disorder (ASD) has continued to increase over the past two decades. According to a recent report by the Centers for Disease Control and Prevention (CDC), 1 in 59 children are diagnosed with ASD, with boys being 4 times more likely to be diagnosed than girls (1). The age of diagnosis is typically around 4 years of age, but a child as young as 12

months old can be diagnosed (2). ASD is often characterized by repetitive mannerisms, and deficits in both communication and social behaviors (3). Much of the deficits in communication stem from the delay in the onset of speech, poor understanding of the words being spoken to them, and the inability to use speech appropriately in social situations, such as not answering the question being asked or using an improper tone of voice (4). In addition, children with ASD often have difficulty interpreting sounds or visual information, which may lead to a decrease or lack of response to normal social cues, further hindering the formation of relationships with others (5). These children typically have a difficult time adjusting to new surroundings and stimuli, often favoring their everyday, predictable routines. Even with these common characteristics, managing children with ASD, particularly when they are ill can be difficult as no two children present the same way (6). It is critical that primary care physicians recognize core characteristics of children with ASD as it may translate to earlier diagnosis and intervention, as well as appropriate management when they are unwell (7, 8).

During an acute illness, healthcare providers often face a unique challenge in managing patients with ASD because of their core characteristics. The limited verbal communication, impaired social interaction, repetitive behaviors, aggression, and sensory sensitivities can become barriers to medical diagnosis and management during the visit. In addition, interruption in the child's routine, the new environment and exposure to a multitude of new faces, and encounters may further exacerbate the irritability that even typical children have during an acute illness (9). Environmental stimuli such as the bright lights, noise, smell, and the fast pace of the acute care clinic or Emergency Room (ER) can further compound the sensory processing disorders that many children with ASD have. It is critical that a physician distinguishes the baseline or exacerbated behavior of an acutely ill child with ASD from new medical symptoms that led to the visit in order to prevent misdiagnosis and provide the appropriate management (10). This is particularly challenging in an ER or acute care setting whereby the physician is unlikely to have a previous relationship with the child or family and therefore limited baseline knowledge of the patient or limited insight into how acute illness may affect behavior in children with ASD.

Our overarching hypothesis was that medical students and pediatric trainees would report a gap in their general knowledge of ASD, especially when encountering the sick child with ASD.

METHODS

Setting, Participants and Study Design

All medical students at The University of Alabama at Birmingham (UAB) Medical School and pediatric residents at Children's of Alabama were eligible to participate and invited to complete a survey (via www.surveymonkey.com). One hundred and ninety one medical students and pediatric residents responded to the call for participation and were enrolled in this cross-sectional study. Non-participation was likely due unawareness to the call for participation and time constraint. The survey was distributed via emails, with 2 follow-up emails over a 3-month period. This population was chosen to allow assessment of perceived knowledge base in ASD across training levels (medical students; pediatric interns, residents and fellows).

Participant Variables and Survey Questions

Participant variables collected included level of training for medical students (year 1–4) and pediatric trainees (intern, resident, fellow), trainee age range (21–30, 31–40), ethnicity (Caucasian, African American, Hispanic, Other) and gender (male, female). A 23-question survey (**Appendix**) with questions ranging from general knowledge of children with ASD, including methods of communication, sensory sensitivities, perceived importance for understanding ASD behavior, perceived comfort level in providing care, with focus on differences during acute illness, and perceived adequacy of training in ASD. Several questions required participants to rate their answers on a scale of 1 to 10, with 1 being the lowest score and 10 being the highest score.

Statistical Methods and Analysis

Descriptive statistics were utilized to summarize data including counts and percentages for categorical variables and means and standard deviations for continuous variables. Trends and association in responses and education status and gender were analyzed using Fisher's exact test for categorical responses and Wilcoxon Test for responses requiring rating between 1 and 10. Responses of primary interest were: perceived best method of communication with children with ASD, perceived importance of daily behavior and daily routine, comfortability of treating a child with ASD who presents with an acute illness, the best method to communicate with children with ASD who present with an acute illness, and the perceived best method of education regarding this topic. For the purpose of comparing educational and training level, participants were either in the medical student group or pediatric trainee group. This was done to ensure an adequate amount of data to enable comparisons. All analyses were done utilizing the SAS 9.4 software program. Any p value found to be <0.05 was deemed significant.

RESULTS

One hundred and ninety one survey responses were collected and recorded. Demographics of the participants can be found in **Table 1**. Most of the survey respondents were first year medical students, ages 21–30 years old, and Caucasian. The ratio of men to women surveyed varied on education and training level.

Cross-Sectional Survey Data

General Knowledge of ASD

The perceived general knowledge of ASD was low for both medical students and pediatric trainees. More than 85% of all responders rated their general knowledge of ASD to be less than somewhat informed (**Table 2**). However, with increased training level, a higher proportion of pediatric trainees stated that they have more general knowledge compared to medical students ($p = 0.0494$).

TABLE 1 | Demographics.

Parameters	MS1	MS2	MS3	MS4	Pediatric intern	Pediatric resident	Pediatric fellow	Overall (*N*)
Count (%*N*)	64 (33.51)	29 (15.18)	36 (18.85)	24 (12.57)	9 (4.71)	13 (6.81)	16 (8.38)	191
Age								
21–30	64 (35.96)	28 (15.73)	35 (19.66)	24 (13.48)	8 (4.49)	12 (6.74)	7 (3.93)	178
31–40	–	1 (7.69)	1 (7.69)	–	1 (7.69)	1 (7.69)	9 (69.23)	13
Ethnicity								
Caucasian	55 (34.16)	23 (14.29)	31 (19.25)	18 (11.18)	7 (4.35)	11 (6.83)	16 (9.94)	161
African-American	1 (16.67)	3 (50.00)	1 (16.67)	–	–	–	1 (16.67)	6
Asian	8 (30.77)	5 (19.23)	6 (23.08)	5 (19.23)	1 (3.85)	1 (3.85)	–	26
Hispanic	1 (20.00)	1 (20.00)	–	1 (20.00)	1 (20.00)	1 (20.00)	–	5
Other*	–	–	–	–	1 (100.00)	–	–	1
Gender								
Male	24 (30.38)	11 (13.92)	13 (16.46)	14 (17.72)	3 (3.80)	6 (7.59)	8 (10.13)	79
Female	40 (36.36)	18 (16.36)	22 (20.00)	10 (9.09)	6 (5.45)	6 (5.45)	8 (7.27)	110

**Other means ethnicities not already included.*
MS, medical student.

TABLE 2 | Perceived general knowledge of ASD.

	No information	Limited information	Somewhat informed	Very informed
Medical students	2.61%	42.48%	47.06%	7.84%
Pediatric trainees	0%	21.05%	65.79%	13.16%

Interaction With Children With ASD

Medical students had significantly less interaction with children with ASD when compared to pediatric trainees (39.5% limited to no interaction vs. 83.0% monthly, weekly or daily interaction, $p < 0.0001$). In this cohort of participants, all pediatric trainees had their interaction in a medical setting, while medical students varied on interaction setting (41.4% medical, 34.5% familial, 24.1% work other than medical).

Managing a Well-Child With ASD

Medical students rated the importance of understanding baseline ASD behavior lower when compared to pediatric trainees (8.41 $\pm$ 1.24 vs. 9.05 $\pm$ 1.06 on a 1–10 scale, $p = 0.004$). There was no significant difference found in the perceived importance of understanding the daily routine of ASD children for medical students and pediatric trainees (8.73 $\pm$ 1.32 vs. 8.92 $\pm$ 1.28 on a 1–10 scale, $p = 0.338$). As a whole, females participants rated understanding ASD behavior higher than their male counterparts (8.79 vs. 8.16 on a scale of 1–10, $p = 0.005$). They also had a higher rating for understanding the importance of ASD routine (8.95 vs. 8.48 on a scale of 1–10, $p = 0.0107$), as well as discussing the child's routine with the family (8.87 vs. 8.33 on a scale of 1–10, $p = 0.0028$).

In terms of communication, medical students and pediatric trainees selected visual aids and hand motions, followed by verbal communication, eye contact and written words for what they *perceived* to be the primary method of communication that children with ASD use [126 (30.1%) visual aids, 124 (29.6%) hand motions, 76 (18.1%) verbal communication, 32 (7.6%) eye contact, 46 (11.0%) written word, and 15 (3.6%) 'other']. Other responses included using sounds and gestures, an iPad program, and art. However, for best method of communication to use *with these* children, participants chose visual aids (87, 51.2%), verbal communication (43, 25.3%), hand motions (10, 5.9%), written word (10, 5.9%), eye contact (9, 5.3%), and other (11, 6.5%), respectively (**Figure 1A**). Other responses included 'following the child's lead' and singing.

Managing the Sick Child With ASD

More pediatric trainees have provided care to children with ASD compared to medical students (73.7% vs. 15.7%, $p < 0.0001$), with in-patient hospital setting being the most common location for the encounter. Overall, both medical students and pediatric trainees were uncomfortable with providing care to a sick child with ASD (6.63 $\pm$ 1.55 vs. 4.61 $\pm$ 2.19 on a scale of 1–10, $p < 0.0001$). The medical students and pediatric trainees perceived hand motions, visual aids, verbal communication, eye contact, and written words to be the primary method of communication utilized by sick ASD children [124 (34.4%) hand motions, 108 (29.9%) visual aids, 62 (17.2%) verbal communication, 28 (7.8%) eye contact, 25 (6.9%) written word, and 14 (3.9%) other, respectively]. Other responses included talking to the parents and placing the child in the most familiar environment as possible. A similar trend was noted in the best method to communicate *with* them during an acute illness when compared to communication with a well-child [90 (51.1%) visual aids, 42 (23.9%) verbal communication, 17 (9.7%) hand motions, 9 (5.1%) eye contact, 8 (4.5%) written word, and 10 (5.7%) other; **Figure 1B**].

Sensory Dysregulation

Medical students had a significantly lower rating in the understanding of the sensory issues that can occur in children with ASD when compared to pediatric trainees (3.76 $\pm$ 2.54 vs. 5.16 $\pm$ 1.83 on a scale 1–10, $p = 0.0007$; **Figure 2**), but both education groups scored their understanding low overall.

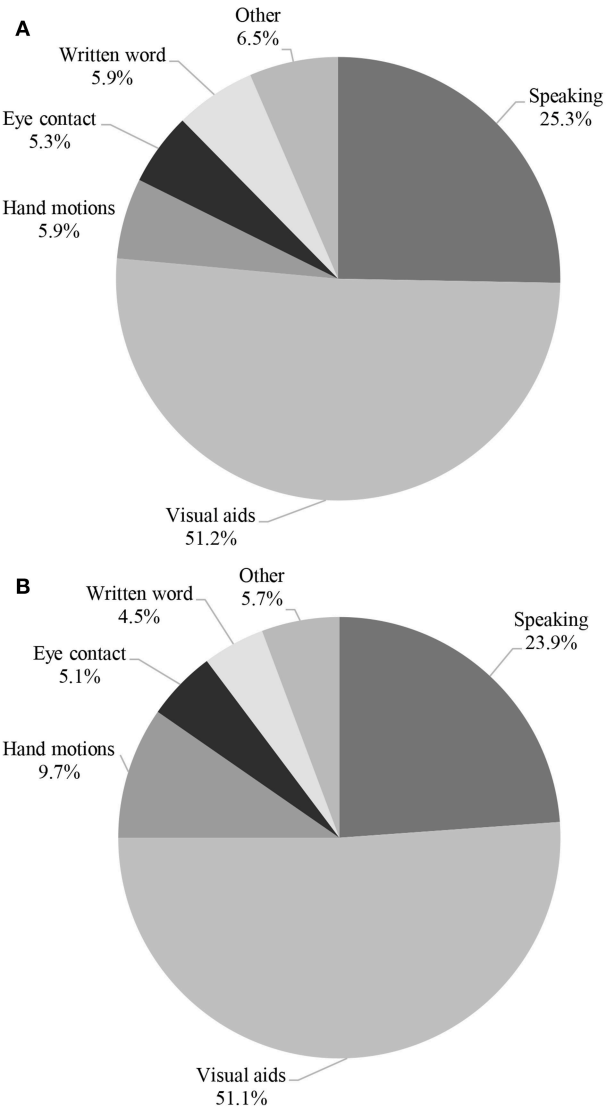

FIGURE 1 | Perceived Best communication method with children with ASD at baseline **(A)** and with **(B)** an Acute Illness.

Medical students also believed that children with ASD experience sensory dysregulation less frequently than pediatric trainees (6.95 ± 1.55 vs. 8.19 ± 1.22 on a 1–10 scale, $p < 0.0001$; **Figure 3**). Both medical students and pediatric trainees felt that it was important to elicit information regarding a child's routine when he or she is presenting with an acute illness (8.68 ± 1.44 vs. 8.61±1.55 on a 1–10 scale, $p = 0.9945$).

Learning About ASD

91.4% of medical students and pediatric trainees reported that they did not received enough didactic or clinical training regarding treatment of a child with ASD when they present with an acute illness, and 92.6% felt that more training on this topic was warranted. When queried regarding ideal training methods, most selected interaction with children with ASD (162, 41.2%), followed by small group sessions (99, 25.2%), didactic lecture (90, 22.9%), role-playing (33, 8.4%), and other methods (9, 2.3%) (**Figure 4**). Other methods included working with parents of children with ASD, learning from other subspecialties such as occupational therapists, and special courses in medical school designed around this topic. Lastly, a higher number of female participants believed that they needed more training on children with ASD (96.3 vs. 87.0%, $p = 0.0235$).

DISCUSSION

With the increasing prevalence of ASD (11), it is critical that healthcare providers have a solid foundation on issues unique to these patients, particularly when they present with an acute medical illness. In this single center study, assessing the perceived general knowledge of ASD in medical students and pediatric trainees, we found that in general, all learners reported a lack of knowledge, had a perceived discomfort in managing medically ill children with ASD, coupled with a desire for more training in this space.

Overall, the perceived general knowledge of ASD was low in both medical students and pediatric trainee (**Table 2**). However, the pediatric trainees reported more knowledge than the medical students. More training, education, and exposure on the topic and patients most likely accounted for the increase in knowledge seen in the pediatric trainees. Without emphasizing this common disease state in the curriculum, we risk misunderstanding of presentations and failures of communication on the wards that may be detrimental to the care process of this increasingly recognized condition.

Children with ASD are partial to routine and order. Disruption of a daily routine can cause a child to become distressed, making it more difficult to communicate with him or her (12). Both medical students and pediatric trainees rated the importance of understanding the baseline behavior of a child with ASD high, with a higher rating given by the pediatric trainees. Similarly, both groups rated the importance of daily routine for ASD children as high. It is imperative that clinicians understand the baseline behavior of their patients, as well as having an appreciation of the importance in routine disruption (13). This is especially important in an acute care setting such as the ER where patients may be interacting for the first time with specific providers. Frontline physicians need to make the assessment for baseline behaviors (often can be elicited via directed questions during history taking) a necessary step in their management of the acutely ill child.

Communication can often become a barrier in providing care to children with ASD. In a recent study, Solomon et al reported that clinicians often rarely spoke to their pediatric patients with ASD during primary or acute care visits (14). In another study, Nicolaidis et al. found that adults with ASD often reported lower satisfaction rates with the quality of communication with their healthcare provider, when compared to neuro-typical adults without ASD (15). Understanding non-verbal communication, and effective use of this communication method is important as it may potentially facilitate better overall care for patients with ASD

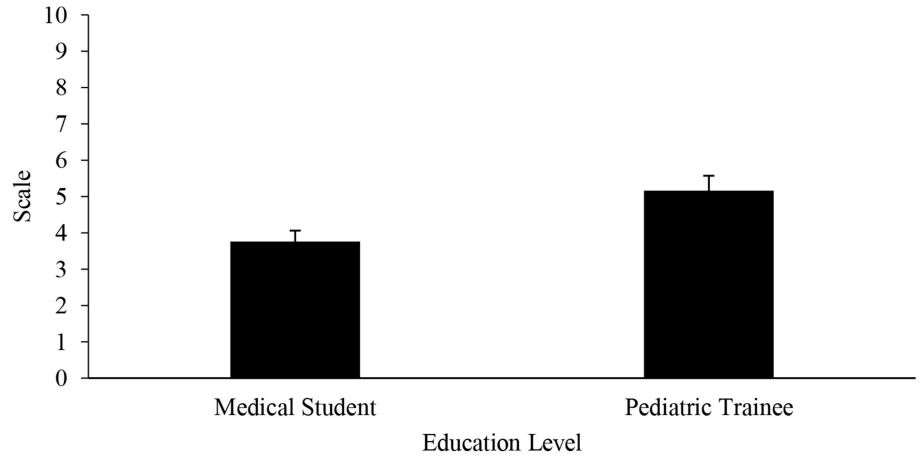

FIGURE 2 | Understanding of sensory dysregulation in children with ASD.

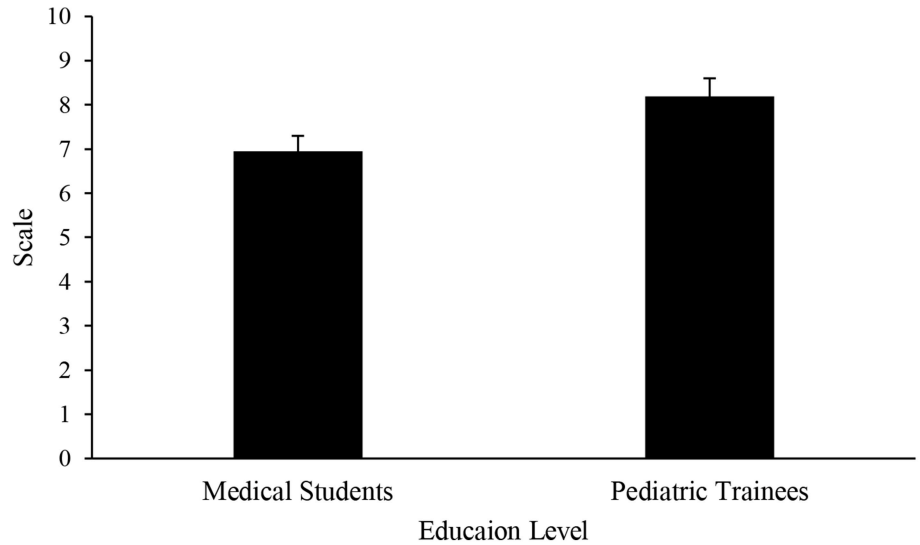

FIGURE 3 | Perceived frequency of sensory dysregulation in children with ASD.

(16–18). Examples of non-verbal communication includes use of drawings, exaggerated hand gestures, use of full body movements and appropriate props (16, 17). In our surveyed population, more than 50% of medical students and pediatric trainees elected using visual aids as the preferred method of communication with a child with ASD. However, approximately a quarter of the surveyed participants selected verbal communication as the preferred method, which may potentially pose a challenge since verbal communication is often not an effective communication tool for patients with ASD (**Figure 1**). Taken together, our findings suggest that additional training in optimal methods of communication is needed among the surveyed trainees. This training will be a critical piece of the skill set necessary for successfully managing acute illness in children with ASD.

Sensory dysregulation is an important core feature of children with ASD (19–21). However, in our surveyed population, although the pediatric trainees reported a higher understanding of sensory regulation compared to medical students, the mean rating was overall low at 5 (out of 10, 10 being the highest rating score; **Figure 2**). Compared to pediatric trainees, medical students rated the frequency of sensory dysregulation in children with ASD to be lower (**Figure 3**). This finding highlights the need for increased awareness of the implications of children with ASD having sensory challenges, particularly when they present with an acute illness (22, 23). In a pilot study of a community zoo, implementation of a sensory training program resulted in more visitations to the zoo by children with ASD and a better overall experience for the child, families, and staff members (24). Staff training included ways to identify a guest with sensory sensitivity, methods of communication and engagement, as well as techniques to handle situations when a child was in sensory overload. It may be posited that a training

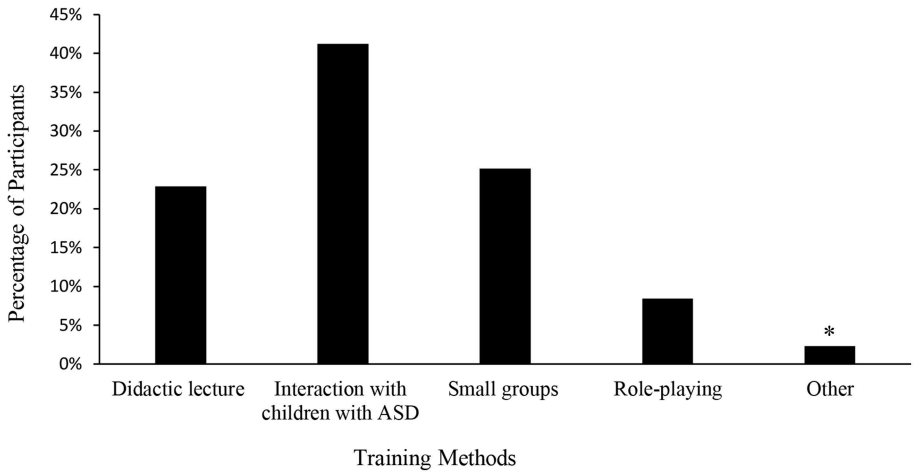

FIGURE 4 | Perceived Best Training Method of Learning by Medical Students and Trainees. *Other: working with parents of children with ASD, learning from other subspecialties such as occupational therapists, and special courses in medical school.

program with a focus on sensory processing challenges may be beneficial for medical providers. Such a program will increase the understanding of sensory sensitivities that are often heightened during acute illness and will provide communication techniques, as well as potentially allowing for tangible modification of the environment (for instance provision of sensory tools such as noise canceling headphones). The goal is ultimately to mitigate these sensory barriers that may hinder appropriate and timely diagnosis or management, as well as improve patient satisfaction and service.

Clinicians in general report an increased feeling of discomfort when having encounters or managing patients with ASD (24–29). In our study, more than 90% of medical students and pediatric trainees reported insufficient didactic and clinical training for managing a child with ASD who presents with an acute illness. Similarly, more than 90% reported the need for increased training in this arena. Interestingly, there was no difference across training levels in the reported need for more training, with pediatric trainees reporting the need just as frequently as first year medical students. Across all training levels, interaction with children with ASD was the most frequently selected option for best method of teaching, followed by small group learning (**Figure 4**). Others have shown that facilitated direct encounters with children with ASD could potentially increase the comfort level of trainees for future encounters with ill children with ASD who present in a hospital setting (30, 31). Creating a pediatric training curriculum centered around patient interactions and small group learning could provide the knowledge necessary in a format preferred by students, to properly treat children with ASD when they present with acute illnesses (32, 33).

In this single center study, we identified several limitations. First, the sample size is small as the research was conducted in one academic medical institution and the partnering children's hospital. A survey bias could have occurred due to convenience sampling, and the overall low response rate from certain groups, therefore affecting the potential generalizability of the results. However, these initial data are important as they will inform the design of a large prospective study involving not just physicians but other providers such as nurses, that will provide more granularity to the deficits identified and how widespread they are. The participants were also not evenly distributed among each level of training. In our analysis, medical students were grouped and compared with pediatric trainees. Because most of the medical students (33.5%) were from the first year, it did naturally allow for comparison between the lowest level trainee (first year medical student), and the highest-level trainees (pediatric fellows). Lastly, the questions asked on this survey were not exhaustive to the information that could have been collected. More areas of limited understanding on ASD may exist but were not covered in this study.

CONCLUSION

The findings of this study suggest that medical students and pediatric trainees across all levels perceived a lack of knowledge regarding ASD. Medical students and pediatric trainees also reported increased discomfort and need for increased education and training in relation to the treatment of children with ASD who present with an acute illness. Taken together, this study highlights current gaps and underscores the importance of ensuring adequate knowledge and training for medical professionals particularly as it relates to improving our ability to care for medically ill patients with ASD.

ETHICS STATEMENT

This study was performed with the University of Alabama at Birmingham institutional review board (IRB) approval (Protocol E160414004) and carried out with voluntary and electronic informed consent from all study participants. Survey respondent anonymity was ensured by not collecting any personally

identifiable information. All data were stored in a password-protected server.

AUTHOR CONTRIBUTIONS

KA created the survey, collected and analyzed the data, and contributed toward the writing of the manuscript. IA, JW, and MK analyzed and interpreted survey results and contributed toward the writing of the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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When Local Bone Pain Is Just the Tip of the Iceberg—A Case Report of Three Patients With Chronic Multifocal Recurrent Osteomyelitis and Some Red Flags to Help Make the Diagnosis

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Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon cause of chronic inflammatory bone pain in children that can be disabling. Often, this diagnosis is considered only after a prolonged workup, leading to frustration for families and unnecessary interventions for patients. Here we describe three cases of CRMO to increase awareness of how it may present. The first patient had a typical presentation of focal bone pain (knee), for which she underwent bone scan (hint of >1 lesion), had a bone biopsy to rule out malignancy, received empiric antibiotics for presumed infection, and finally had whole-body imaging confirming CRMO when symptoms persisted. The second patient had a similar workup, but initially presented with clavicular pain. This location should raise suspicion for CRMO, as it is an uncommon location for infectious osteomyelitis. The third patient presented with delayed growth and right hip pain, and simultaneously developed palmoplantar pustulosis. These secondary findings can also serve as red flags for CRMO, as it has been linked to this skin condition and inflammatory bowel disease. All patients improved on non-steroidal anti-inflammatory (NSAID) medications, methotrexate, and/or tumor necrosis factor (TNF)-α antagonists. By raising awareness of clinical findings suggestive of CRMO, this report may help expedite diagnosis, so patients can be started on anti-inflammatory therapy.

Keywords: chronic non-bacterial osteomyelitis, pustulosis, inflammatory bowel disease, pediatric, bone pain

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INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory disease in children with a reported incidence of 0.4 per 100,000 (1). Most patients have a disease onset between 7 and 12 years of age, and girls are disproportionately affected (2). Clinical presentation involves at least one region of focal bone pain that may cause functional impairment. Symptoms may relapse and remit, and the affected region can migrate between one flare and the next (3). Often full body imaging will reveal ≥4 lesions of osteomyelitis, particularly in the lower extremities, vertebrae, and clavicles (4, 5). CRMO is also affiliated with other inflammatory processes, particularly inflammatory bowel

disease (IBD), spondylitis, psoriasis, and palmoplantar pustulosis (2, 6). The most significant clinical consequences for children include chronic pain and disability, leg length discrepancy (if lesions involve the growth plates), and failure to thrive (if associated with IBD) (7, 8). Once started on anti-inflammatory medications, the disease is often self-limited and usually resolves after a few years (3).

There are several diagnostic challenges for CRMO, which all inter-relate. First, even if a patient has multiple bone lesions, not all will have related symptoms of pain or tenderness. In addition, even in affected symptomatic areas, the lesions are often undetectable on plain radiographs. Whole body MRI (WBMRI) is the standard diagnostic modality, because it can reveal the multifocal, often symmetric nature of the disease and symptomatic and asymptomatic areas of involvement. However, when there is only one region of pain on presentation, the differential diagnosis in children is quite wide, including many conditions that are far more common and better known than CRMO (**Table 1**). Thus, it is not always obvious that a WBMRI is warranted. As a final challenge, there are no universally accepted diagnostic criteria for CRMO, although some have been suggested (**Tables 2**, **3**) (9, 10). Altogether, these challenges mean that diagnosis often entails an extensive and prolonged workup by multiple specialists, and children may have been exposed to prolonged courses of antibiotics, which can lead to adverse effects and antimicrobial resistance. There are likely many cases that have never been diagnosed (7, 9).

Over the last 5 years, one of the authors (L.I.) has diagnosed nine cases of CRMO. Each case presents uniquely, and often families come with prolonged journeys to diagnosis. The goal of this report is to highlight three representative cases that help to familiarize community pediatricians with some common attributes of this rare and debilitating disease. All cases are presented after signed consent from patients and their guardians (if <18) for presentation of de-identified data. The study was further approved by an IRB protocol at Columbia University Medical Center (AAAS 3818).

CASE PRESENTATIONS

Case A

Patient A was an otherwise healthy 10-year-old girl who participated in competitive figure skating. She experienced insidious onset left knee pain, which was 8/10 in severity and only moderately improved with ibuprofen. Her family initially thought this could be related to skating and waited for it to disappear. However, the pain persisted, and she developed a limping gait. She had no fevers or rash, nor recent illnesses, travel, or tick exposure.

Her pediatrician referred her to orthopedics, who noted pain out of proportion to exam and ordered imaging. MRI of the left knee showed an intramedullary lesion in the proximal tibial and distal femoral metaphyses surrounded by edema and inflammation (**Figure 1**). Due to concern for potential malignancy, she was referred to oncology who ordered a technetium 99m-MDP bone scan and CT-guided biopsy. The bone scan was not consistent with acute osteomyelitis, with only mild radio-tracer uptake in the tibial lesion. Curiously, there was also a region of increased avidity in the posterior second rib. Subsequent tibial biopsy showed an inflammatory process in the marrow space extending to the growth plate. All cultures were negative.

The patient was referred to specialists in infectious disease whose differential diagnosis included acute bacterial osteomyelitis vs. CRMO. Due to elevated inflammatory markers, the patient was started on an empiric trial of antibiotics. Over the course of the next few months, her pain decreased, and her inflammatory markers and lesion on MRI imaging improved. The antibiotics were then discontinued after 4 months. Her knee pain remained quiescent for another 7 months but then recurred. Repeat MRI showed exacerbation of the tibial lesion, and repeat biopsy was again negative for growth of organisms. She was subsequently referred to our rheumatology practice for workup of CRMO (1 year after disease onset).

On initial visit, she had tenderness to palpation of the lateral proximal tibia. Her range of motion was fully intact, and inflammatory markers were, at this point, normal. WBMRI revealed lesions in eight regions, including her posterior rib (previously seen on bone scan), T9 vertebral body, bilateral sacroiliac joints, bilateral distal femoral metaphyses, and bilateral proximal tibial metaphyses. She was started on indomethacin, which provided some benefit but did not completely eliminate her pain. Methotrexate was added along with a brief course of oral prednisone, since glucocorticoids can help prevent vertebral collapse in the setting of spinal lesions (11, 12). She developed new bone lesions while on therapy and was switched to adalimumab (TNF-α inhibitor). She is not currently

TABLE 1 | Differential diagnosis for presentation of bone pain ± fever.

Infectious	Malignant	Traumatic	Auto-immune/ inflammatory	Other
- Bacterial osteomyelitis - Fungal osteomyelitis (coccidioidomycosis, cryptococcosis) - Brucellosis - Pott's Disease *(M. tuberculosis)*	- Osteoid osteoma - Osteosarcoma - Ewing sarcoma - Leukemia - Lymphoma - Langerhans cell histiocytosis - Skeletal metastases	- Bone bruise - Fracture - Stress injury	- CRMO - Juvenile Idiopathic Arthritis	- Gaucher's Disease - Sickle cell disease - Avascular necrosis

TABLE 2 | Jansson criteria for diagnosis of CRMO.

Major diagnostic criteria	Minor diagnostic criteria
1. Radiologically proven osteolytic/-sclerotic bone lesion 2. Multifocal bone lesions 3. Palmoplantar pustulosis (PPP) or psoriasis 4. Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	A. Normal blood count and good general state of health B. CRP and ESR mildly-to-moderately elevated C. Observation time >6 months D. Hyperostosis E. Associated with other autoimmune diseases apart from PPP or psoriasis F. Grade I or II relatives with autoimmune or autoinflammatory disease

Non-bacterial osteomyelitis (i.e., CRMO) is confirmed by 2 major or 1 major + 3 minor criteria.

TABLE 3 | Bristol Criteria for diagnosis of CRMO.

The presence of typical clinical findings (bone pain ± localized swelling without significant local or systemic features of inflammation or infection)

AND

The presence of typical radiological findings (plain x-ray: showing combination of lytic areas, sclerosis and new bone formation, or preferably STIR MRI: showing bone marrow edema ± bone expansion, lytic areas, and periosteal reaction)

AND EITHER

Criterion 1: >1 bone (or clavicle alone) without significantly raised CRP (<30 mg/L)	Criterion 2: if unifocal disease (other than clavicle), or CRP >30 mg/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis, or sclerosis) with no bacterial growth while not on antibiotic therapy

experiencing any of her pain and has returned to figure skating competition.

Case B

Patient B was a 10-year-old girl with a history of scoliosis and hypothyroidism, whose family was living in Europe at the time of symptom onset. She was playing with a sibling and experienced significant pain when poked in the left clavicle. There was no fever or swelling, but the pain persisted, and her primary pediatrician referred her to orthopedics. Radiographs showed no evidence of fracture or dislocation, and she was prescribed ibuprofen. This did not provide relief, as she continued to have intermittent clavicular pain and occasional jaw pain.

She tolerated this discomfort into the next year when her endocrinologist decided to admit her for further workup. Lab evaluation showed elevated inflammatory markers, and she was given antibiotics, which did not lead to symptomatic improvement.

Her family moved back to the United States and visited a hospital, where they were told that she had chronic osteomyelitis and that it would resolve with time. They sought a second opinion at another hospital, where a bone biopsy was performed, which showed no evidence of infection. Her inflammatory markers were still elevated, and she was again trialed on antibiotics. As with before, this did not yield improvement, and they were discontinued due to gastrointestinal intolerance.

FIGURE 1 | Multiple metaphyses affected in the left knee. Coronal proton density (MRI) image shows multiple areas of abnormality extending from the physes into the metaphyses of the distal femur and proximal tibia.

FIGURE 2 | Involvement of the left clavicle. Radiograph obtained 2 years after disease onset showing that the left clavicle is broader and denser than the right, indicating chronic changes.

She then visited a third hospital, where a rheumatologist clarified her diagnosis as CRMO (3 years after disease onset). She was initially treated with indomethacin but discontinued it due to headaches. Over the next few years, she controlled her flares with ibuprofen. Eventually she established care with a new rheumatologist who started her on sulfasalazine, but this was discontinued.

Over time, her jaw pain worsened, and repeat MRI showed evidence of mandibular lesions. Etanercept (TNF-α inhibitor) was trialed and did not help, and after moving cities, her new pediatrician prescribed high dose steroids and referred her to our practice (7 years after disease onset).

At the time of initial visit, she continued to complain of jaw pain and swelling. Physical exam was positive for jaw edema, and

FIGURE 3 | Involvement of the proximal right femur. Anterior-posterior radiograph shows a well-defined lucent lesion in the proximal diaphysis of the right femur with surrounding sclerosis, indicating chronic osseous destruction.

tenderness over the left clavicle (**Figure 2**). There was no loss in range of motion. WBMRI revealed an additional lesion in her right clavicle, and she was started on adalimumab, on which she has had improvement in inflammatory markers and pain level.

Case C

Patient C was also a 10-year-old girl, who was otherwise healthy other than exhibiting poor growth. At baseline, she was involved in gymnastics; however, this changed when she started to experience right hip pain. This pain persisted at all times of day and was partially relieved by ibuprofen. It was never in the left hip or knees, but she reported some discomfort in her ankles. She had no fevers but developed a transient pustular rash on her palms and soles.

As the pain became increasingly disabling, she developed a limp. She was referred to orthopedics, who prescribed crutches and obtained a hip MRI. This showed a lesion in the right medial proximal femur (**Figure 3**). A bone scan was then performed to look for additional lesions, but none were found. Biopsy of the lesion was consistent with osteomyelitis but was undifferentiated between an infectious vs. inflammatory cause. The patient was thus referred to both infectious disease and rheumatology.

Infectious disease specialists suggested that the patient's presentation was more consistent with CRMO than bacterial osteomyelitis, given the chronicity and negative culture on biopsy. Our rheumatology team came to the same conclusion (1-year after symptom onset). When we saw the patient, she was tired and pale appearing, with thinning hair. Her BMI percentile was 1%. Musculoskeletal examination was notable for tenderness in the sacroiliac region and right femur, as well as reduced range of motion of her ankles. There were no skin lesions at the time of our exam. WBMRI showed lesions in her proximal right humerus, proximal right femur, bilateral proximal tibias, and bilateral distal femurs. She was treated with indomethacin and has since clinically improved.

Given her history of poor growth, a fecal calprotectin was performed to screen for IBD and was positive. This led to a colonoscopy, which showed granulomas throughout her intestinal tract (Chronic Granulomatous Disease was evaluated and excluded). She was given the diagnosis of Crohn's disease despite her lack of gastrointestinal symptoms. Her CRMO treatment was advanced to adalimumab, which treats both disease processes, and she has symptomatically improved.

DISCUSSION

The above cases are representations of how challenging it is to diagnose CRMO, often involving many specialists over the course of months to years. Our recounting of patient narratives does have limitations. By the time patients reach our rheumatology practice they have had a long workup, and we cannot corroborate all the details of their prior encounters with physicians at different hospitals. To shorten the time to diagnosis, we aim to describe some findings within our patients' histories that can raise the index of suspicion for CRMO and to describe the relevant literature.

All of our patients were 10-year-old females. This is more than coincidence, as CRMO is more likely to affect females than males (2:1), and most studies report a median age of onset around 10 or 11. All patients presented initially with one predominant area of pain, although there were hints that something else could be amiss.

Patient A had a very typical workup for CRMO including: local imaging, bone scan (hint of a 2nd rib lesion), and bone biopsy. The main differential diagnoses from the beginning were CRMO and bacterial osteomyelitis. As with patient B, she was trialed on empiric antibiotics in the setting of elevated inflammatory markers (ESR/CRP), even though her bone cultures were negative, and she had been afebrile.

In a case-matched study between bacterial osteomyelitis and CRMO (4), CRP was more characteristically elevated in bacterial osteomyelitis than CRMO (CRP 31 $\pm$ 50 vs. 9.8 $\pm$ 15.9 mg/dl, (mean $\pm$ SD), $p = 0.008$), and fever was present in 38% of cases vs. 12% ($p = 0.003$), respectively. Other reports have found elevated inflammatory markers in 40–70% of CRMO patients (1, 9). Thus, the presence of elevated inflammatory markers does not, alone, distinguish between infection or CRMO such as with Patients A and B.

The other potentially discriminating feature between bacterial and inflammatory osteomyelitis in these patients was their culture-negative biopsies. It is not surprising that these results were interpreted cautiously. *Staphylococcus aureus* and *Streptococcus pyogenes* are some of the most common bacterial pathogens in childhood osteomyelitis over the age of five. However, it is not uncommon for (presumed) infectious

osteomyelitis to show no growth of organisms (13). Given infectious osteomyelitis is >20 times more common than CRMO and carries the potential for devastating sepsis if left untreated, many physicians will opt for empiric, broad-spectrum antibiotics if there is any ambiguity in diagnosis. While antibiotics can effectively treat culture-negative infectious osteomyelitis, they are less helpful for CRMO, which resolves with anti-inflammatory agents (14, 15). Thus, it is important to continue to follow these patients to ensure symptomatic resolution from their antibiotic course.

Patient A's clinical course was obscured by the fact that she did appear to improve after antibiotics. In retrospect, this may have reflected the relapsing and remitting course of CRMO symptoms. With a complaint as non-specific as knee pain, a diagnostic workup similar to Patient A may have been inevitable; however, in the setting of an afebrile, otherwise well-appearing patient, with chronic pain, hints on bone scan of more than one lesion, and a negative bone culture, CRMO should at least be on the differential (as it was for this patient).

The most salient feature of Patient B's history was her initial presentation with clavicular pain. Although the most common region for CRMO lesions is the long bones of the lower extremities, the clavicle is also characteristic, whereas it is an extremely uncommon location for bacterial osteomyelitis (4, 9). Patient B was eventually found to have bilateral clavicular lesions. While this finding came after diagnosis, it also reflects two unique features of CRMO—the presence of multifocal lesions as well as symmetric lesions (16).

Patient C's workup had several features suggestive of an underlying systemic inflammatory process. First, she had a history of poor growth. This led to a suspicion of IBD, as this condition is seen in ∼10% of patients with CRMO. Despite her lack of overt symptoms, the bowel inflammation that was eventually diagnosed by endoscopy may have preceded her CRMO, explaining her failure to thrive (17). The other red flags in her history were her skin findings of palmoplantar pustulosis and her sacroiliac pain, findings seen in 8 and 25% of CRMO patients, respectively (2).

All patients underwent local imaging and biopsy during workup. Although the results do not always discriminate between infectious and inflammatory osteomyelitis, diagnosis of CRMO can often be confirmed if whole body imaging is performed. In light of this, one approach may be to perform WBMRI at an earlier time point. There is currently no algorithm for when such a study is likely to have the highest yield and cost-effectiveness based on a pre-test probability; however, there are potentially unique local imaging features that could help, which is currently under investigation by our team.

As another possible solution, other groups have been evaluating novel laboratory measures, since white blood cell count and ESR/CRP are non-specific. A study from 2013 divided patients into: (1) confirmed pyogenic, (2) presumed pyogenic, and (3) inflammatory osteomyelitis/arthritis. A serum procalcitonin threshold of 0.4 ng/mL had a 85.2% sensitivity and 87.3% specificity in discriminating groups 1+2 from group 3, suggesting that procalcitonin could be a useful diagnostic tool to diagnose infectious vs. inflammatory osteomyelitis (18).

Once diagnosed, first line treatment involves NSAIDS, particularly indomethacin and naproxen. On such a regimen, >50% of patients will experience clinical improvement within 12 months, as described in detail by Beck et al. (19). The Childhood Arthritis and Rheumatology Research Alliance (CARRA) has proposed 3 second line strategies: (1) methotrexate or sulfasalazine, (2) TNF-α inhibitors ± methotrexate, and (3) bisphosphonates (12). These can be used in addition to NSAIDS or can replace them if patients cannot tolerate the gastrointestinal side effects. Finally, bisphosphonates or short courses of steroids should be considered for patients with spinal lesions who are at risk of vertebral collapse.

CONCLUSION

In summary, CRMO is an autoinflammatory disease of the bone in children that can cause chronic debilitating pain and disability. CRMO has onset around age 10 and affects girls more than boys in a 2:1 ratio. While rare, it is likely underdiagnosed, and better awareness may help reveal missed diagnoses and expedite care. Clues toward CRMO from patient histories and workup include: chronic bone pain, culture negative biopsies, clavicular pain, and systemic inflammatory features such as IBD. Conversely, if a diagnosis of CRMO has been made, it is important to screen for these other features, as IBD can be detrimental to growth and development. While children may have different medication tolerances, most do well on NSAIDs, methotrexate, and/or TNF-α inhibitors. Systemic steroids are not usually necessary but may be indicated if the lesions involve vertebral bodies or have caused a bone fracture. The natural history for most patients is for the disease to be self-limited.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by an IRB protocol at Columbia University Medical Center (AAAS 3818). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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West Syndrome in an Infant With Vitamin B12 Deficiency Born to Autoantibodies Positive Mother

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Infantile vitamin B12 deficiency, a rare nutritional disorder in developed countries, is characterized by megaloblastic anemia and non-specific symptoms, including failure to thrive, hypotonia, and seizure. Symptoms usually develop at 6 months of age. Exclusively breast-fed infants of vegan-diet mothers are particularly at risk. We report the case of a 7-month-old boy with West syndrome born to a mother with subclinical vitamin B12 deficiency due to autoantibodies. Electroencephalography revealed the characteristic hypsarrhythmia pattern, whereas cranial magnetic resonance imaging revealed cerebral atrophy and hypomyelination. Biochemical analysis revealed elevated urinary methylmalonic acid and homocysteine and reduced plasma methionine. Serum vitamin B12 levels were extremely low in both the child and his mother. The mother tested positive for both anti-intrinsic factor and anti-parietal cell antibodies. Low-dose adrenocorticotropic hormone was effective for seizure control. Contrary to previous reports, age-appropriate neurodevelopment was not achieved despite rapid normalization of metabolic profile with vitamin B12 supplementation. Further investigations failed to detect any causative mutations in the genes associated with developmental and epileptic encephalopathy as well as metabolic and other identifiable disorders known to cause West syndrome. To the best of our knowledge, this is the first reported case in which maternal anti-intrinsic factor antibody was considered to be the reason for infantile vitamin B12 deficiency with West syndrome. Differential diagnosis of West syndrome should include vitamin B12 deficiency due to its treatable nature, and early diagnosis is essential to prevent permanent neurological consequences.

Keywords: west syndrome, infantile spasm, cobalamin, anti-intrinsic factor antibody, anti-parietal cell antibody

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BACKGROUND

West syndrome, an age-related epileptic disorder affecting children during infancy and early childhood, is characterized by epileptic spasms occurring in clusters and prominent interictal epileptiform discharges (1). Children with West syndrome have a high risk of developing cognitive deterioration, thereby warranting early and aggressive anti-epileptic treatment. Many conditions

are associated with this heterogeneous disorder, including early brain insults, malformations, chromosomal anomalies, inborn errors of metabolism, and mutations or genomic deletions in disease-associated genes (1). Despite its rarity, early diagnosis of metabolic disorders, such as phenylketonuria, Menkes disease, and pyridoxine deficiency, is important since it may result in a specific treatment (2).

Herein, we describe a case of West syndrome in an exclusively breast-fed infant with secondary dietary vitamin B12 deficiency due to subclinical maternal deficiency. The mother had significant vitamin B12 deficiency despite normal maternal diets. Further investigations revealed the presence of anti-intrinsic factor antibody (AIFA) and anti-parietal cell antibody (APCA) as the underlying etiology.

CASE PRESENTATION

A 7-month-old boy was born at full term after an uneventful pregnancy of 39 weeks. His birth weight was 2,708 g (−1.1 standard deviation scores, SDS) and head circumference was 33.8 cm (0.4 SDS). Expanded newborn screening, including tandem mass spectrometry, detected no abnormalities. He is the second child of healthy non-consanguineous parents, and their family medical history is unremarkable. At 5 months, the patient had missed developmental milestones and became hyporesponsive with decreased general activity. At 7 months of age, he had recurrent episodes of head nodding with sudden extension of the extremities and upward eye deviations occurring in clusters. Although exclusively breast-fed, he showed no

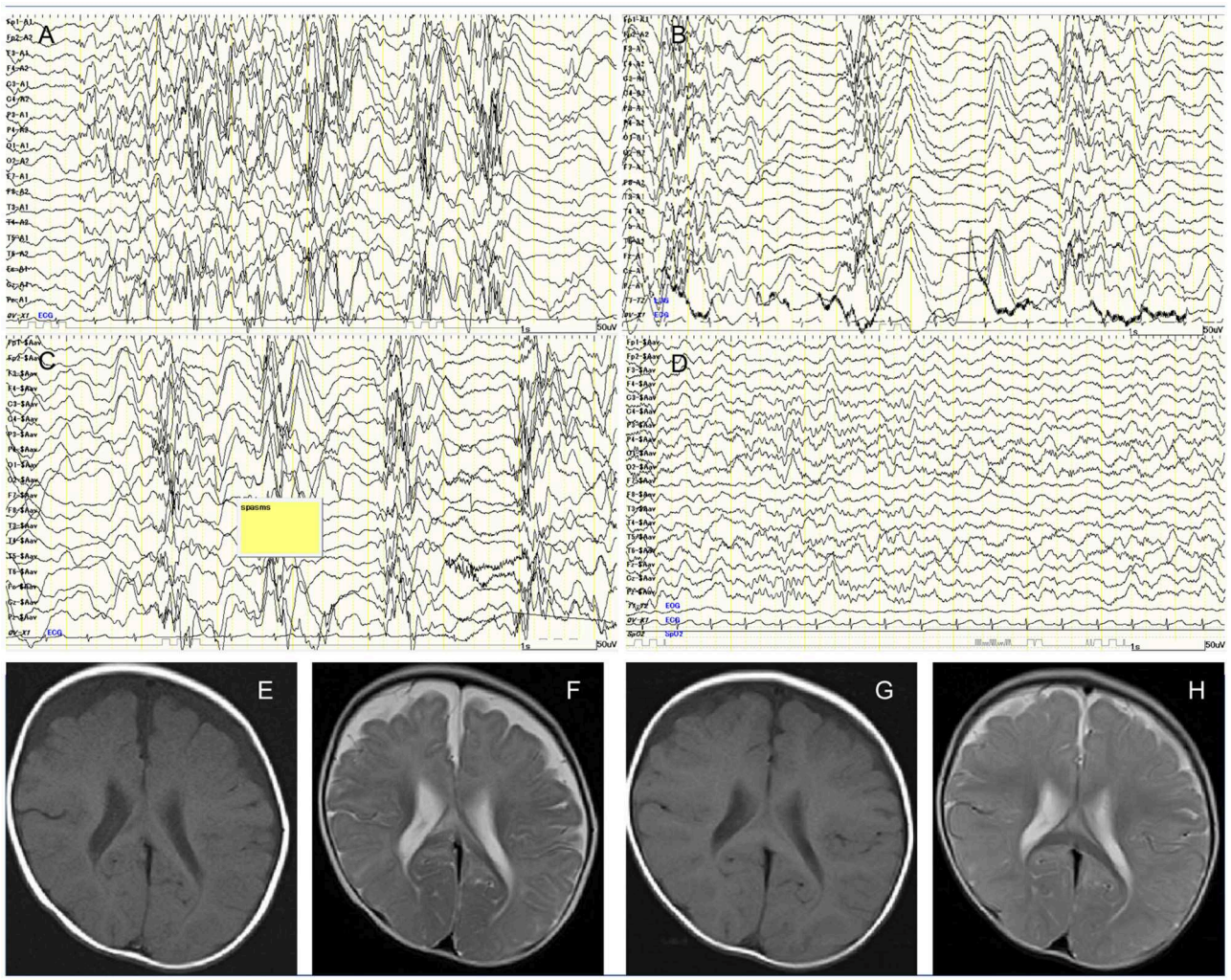

FIGURE 1 | (A) Interictal awake electroencephalography at 7 months showing the characteristic random high-voltage slow waves with spikes and polyspikes activity. **(B)** Fragmentation of the hypsarrhythmic activity is noticed during sleep recording. **(C)** Ictal EEG recording showing a cluster of epileptic spasms with high amplitude slow wave at each spasm. **(D)** Sleep recording showed normalization of background EEG observed 2 months after treatment. **(E)** Axial T1-weighted image. **(F)** Axial T2-weighted image of cranial MRI before initiation of adrenocorticotropic hormone therapy at 7 months of age showing cerebral atrophy with frontal predominance and delay in myelination. Follow-up imaging after vitamin B12 supplementation at 14 months of age documenting improved delayed myelination and cerebral atrophy. **(G)** Axial T1-weighted image. **(H)** Axial T2-weighted image.

other symptoms of malnutrition with proper weight gain and healthy skin. Interictal electroencephalograhy revealed typical hypsarrhythmia patterns during sleep and awake (**Figures 1A,B**). Ictal EEG demonstrated the typical findings of epileptic spasms (**Figure 1C**). Head circumference was 43.7 cm (−0.2 SDS), and cranial magnetic resonance imaging (MRI) revealed cerebral atrophy and delayed myelination (**Figures 1E,F**). Blood count analysis showed non-macrocytic anemia, whereas metabolic analysis documented methylmalonic aciduria, homocystinuria, and low serum methionine, suggesting vitamin B12 deficiency (**Table 1**). Serum vitamin B12 level of <100 pg/mL is considered severely deficient (3); the patient's vitamin B12 level (52 pg/ml) was detected to be profoundly low. Therefore, he was diagnosed with West syndrome associated with vitamin B12 deficiency.

While topiramate (maximum dose; 9 mg/kg/day) did not improve the seizure frequency, intramuscular low-dose synthetic adrenocorticotropic hormone (daily dosage of 0.0125 mg/kg for 2 weeks, gradually tapered off to once every other day for 2 weeks, twice weekly for 2 weeks, and then weekly for 2 weeks) was effective for seizure control. Follow-up EEG at 2 months showed normalization of background EEG (**Figure 1D**). Vitamin B12 replacement therapy was intramuscularly administered to the patient with an initial dose of 1 mg/day. The dose was gradually tapered and subsequently switched to oral supplementation (500 μg/day) after 3 months. The patient became more active and regained social smile after 2 months of supplementation. Although his psychomotor development improved gradually, age-appropriate developmental milestones were not achieved. Denver Development Screening Test revealed that his psychomotor development was as low as 13 months at 20 months of age. Normalization of vitamin B12 level was achieved despite termination of supplementation at 18 months of age.

Normal genetic testing of *MMACHC*, *MMADHC*, *LMBRD1*, and *HCFC1* genes ruled out intracellular cobalamin metabolism disorders, which may present similar metabolic profiles (methylmalonic aciduria, homocystinuria) in the absence of vitamin B12 deficiency (4). Neurological comorbidity of delayed psychomotor development despite vitamin B12 supplementation prompted further evaluation for other genetic etiologies of West syndrome. Chromosomal analysis via G-banding revealed normal male karyotype. Whole-exome sequencing was performed as previously described (5), and no causative *de novo* point mutations in previously known developmental and epileptic encephalopathies-associated genes, including *ARX*, *KCNT1*, *KCNQ2*, *SCN1A*, *SCN2A*, *SCN8A*, *STXBP1*,

TABLE 2 | Biochemical parameters of the mother.

Parameter	Reference value	At diagnosis
Hemoglobin	11.6–14.8 g/dL	12.9
Hematocrit	35–44%	38.3
Mean corpuscular volume	84–98 fL	104.4
Mean corpuscular hemoglobin	28–32 pg	35.1
Vitamin B12	180–914 pg/mL	85
Folic acid	>4.0 ng/mL	6.2
Iron	40–188 μg/dL	100
Ferritin	13–301 ng/mL	5.5
Total iron binding capacity	290–335 μg/dL	349
Total homocysteine	4–14 nmol/mL	22.7
Methionine	19–41 nmol/mL	18
Urinary methylmalonic acid	<20 mmol/mol creatinine	ND
Urinary homocysteine	Negative	ND
Antinuclear antibody	<1:40	<1:40
AIFA	Negative	Positive
APCA	<10 Units	20

AIFA, anti-internal factor antibody; APCA, anti-parietal cell antibody; ND, not detected.

TABLE 1 | Admission and follow-up biochemical parameters of the patient.

Parameter	Reference value*	At diagnosis, 7 months	Vitamin B12 supplementation period (months)				Last follow-up, 20 months
			1	2	3	5	
Hemoglobin	10.5–14.1 g/dL	9.8	11.4	NT	10.8	10.3	11.8
Hematocrit	32–42%	29.4	33.9	NT	33.8	33.1	36.4
Mean corpuscular volume	72–87 fL	86.5	90.6	NT	81.6	73.9	75.4
Mean corpuscular hemoglobin	23–30 pg	28.8	30.5	NT	26.1	23	24.4
Vitamin B12	180–914 pg/mL	51	>1,500	>1,500	>1,500	>1,500	>1,500
Folic acid	>4.0 ng/mL	>22.0	NT	NT	NT	NT	10.6
Total homocysteine	4–14 nmol/mL	NT	3.6	3.1	3.4	NT	3.2
Methionine	19–41 nmol/mL	8.3	22.2	14.5	14.7	31.8	19.2
Urinary methylmalonic acid	<20 mmol/mol creatinine	347.3	ND	ND	ND	0.9	ND
Urinary 3-OH-priopionic acid	<20 mmol/mol creatinine	68.2	8.2	1.4	4.3	3.0	14.2
Urinary homocysteine	Negative (U/mg creatinine)	0.4	ND	ND	ND	ND	ND
AIFA	Negative	Negative	NT	NT	NT	NT	NT
APCA	Negative	Negative	NT	NT	NT	NT	NT

AIFA, anti-internal factor antibody; APCA, anti-parietal cell antibody; ND, not detected; NT, not tested.
**Normal range value of age-appropriate Japanese population was used.*

SPTAN1, *GNAO1*, *GRIN1*, *FOXG1*, *QARS*, *EEF1A2*, *PIGA*, *CDKL5*, *SLC35A2*, *CASK*, *PCDH19*, or *MECP2*, were found. Copy number variants analysis by eXome Hidden Markov Model algorithm detected no pathogenic variant. The ethics committee of Yokohama City University School of Medicine approved the experimental protocols.

The symptom-free mother underwent evaluation for suspected vitamin B12 deficiency. She had a history of iron deficiency anemia and was given iron supplementation during pregnancy. Macrocytosis was present, and serum vitamin B12 level was severely low (85 pg/mL) despite a normal diet (**Table 2**). Normal esophagogastroduodenoscopy finding and pathological findings confirmed the absence of *Helicobacter pylori*-associated atrophic gastritis. Immunological testing showed positive AIFA and APCA.

DISCUSSION

Vitamin B12 (cobalamin) is a water-soluble vitamin mostly found in trace amounts in animal-source foods and acts as an essential cofactor (**Figure 2**) for conversion of methymalonyl-CoA to succinyl-CoA as well as for methylation of homocysteine to methionine (3). Infantile vitamin B12 deficiency is relatively rare in developed countries, and usually occurs in exclusively breast-fed infants of vegan-diet mothers (6). In our present case, immunologically proven maternal APCA and AIFA are the reasons for vitamin B12 deficiency. Negative detection for both APCA and AIFA at diagnosis rules out the involvement of autoantibodies. Transplacentally acquired AIFA in neonatal cases revealed that the antibody titer significantly decreases in subsequent months and disappears at approximately 3 months (7). The lack of elevated maternal antibody documentation in the child is a limitation of this study.

Hematological manifestations of vitamin B12 deficiency comprises macrocytosis, and in severe cases, megaloblastic anemia (8). Typical but non-specific neurological manifestations in infants include hypotonia, psychomotor retardation or regression, seizures, movement disorders, and failure to thrive (8–10). Active transplacental transport causes 2-times higher cord blood vitamin B12 level than the level in the mother at birth (10), leading to occurrence of symptoms at approximately 6 months after depletion of hepatic reserve. The time of disease manifestation and progression depends on the severity of maternal deficiency.

Epilepsy is a rare clinical manifestation of infantile vitamin B12 deficiency (9), although few reports have described its causal association with infantile spasms including West syndrome (11–14). In general, West syndrome prognosis is unfavorable due to frequent neurological comorbidity; however, all five infants with vitamin B12 deficiency-associated West syndrome showed good prognosis with good seizure outcome, and none showed neurodevelopment delay at the last follow-up (11–14). All children were exclusively breast-fed, and all, except one child, were due to maternal vegetarian diet. Maternal APCA was positive with AIFA undetected in the remaining one child (11).

Delayed myelination, demyelination, axonal degeneration, neurotoxic cytokines imbalance, and accumulation of lactate in the brain cells were hypothesized as the underlying

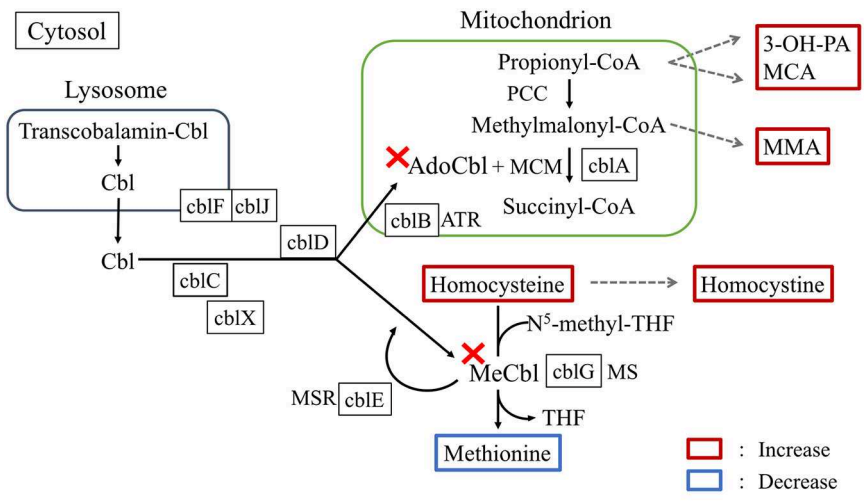

FIGURE 2 | Summarized pathways involving cobalamin metabolism. The map shows the metabolic consequences of vitamin B12 deficiency.

pathophysiological mechanisms for vitamin B12 deficiency in the developing brain (6, 15). Furthermore, the metabolic consequences of homocysteine accumulation and methionine depletion may inflict damages to the central nervous system. Accumulation of homocysteine disrupts the ischemic tolerance by increased oxidated stress and acceleration of atherosclerotic changes (16). A decreased level of methionine causes subsequent low level of S-adenosylmethionine, which functions as a methyl donor acting in a wide variety of biological methylations, resulting in demyelination (17). The initial MRI in our case showed morphological changes of hypomyelination and cerebral atrophy, with further improved MRI findings (**Figures 1G,H**) possibly due to the treatment. Because brain myelination is most active in the first 6 months of life, vitamin B12 deficiency during this period can inflict profound neurological damage. The low maternal vitamin B12 level might have caused irreversible fetal cerebral impairment and subsequently West syndrome in our case. Since the child presented developmental regression from 5 months, West syndrome might have begun much earlier. This delay in diagnosis might offer another possible explanation for the developmental delay despite treatment.

Differential diagnosis of West syndrome should include both genetically inherited metabolic disorders, and "environmentally" acquired metabolic disorders due to autoantibodies or metabolites from untreated mothers. As vitamin B12 deficiency is treatable, clinicians should maintain a high index of suspicion in exclusively breast-fed children presenting failure to thrive, particularly in cases showing seizure or neurodevelopmental delay. Prompt investigation of the child and mother for any comorbidities is also necessary. In the present case, treatment for iron deficiency anemia during pregnancy might have somehow masked the hematological anomaly, thereby causing diagnostic delay of the maternal condition. Infantile nutritional vitamin B12 deficiency can be eminently treatable; therefore, timely diagnosis is warranted to avert permanent neurological consequences.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

Written informed parental consent was obtained for publication of this case report.

AUTHOR CONTRIBUTIONS

PC and RK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. MM, KF, and YW performed the initial analyses and reviewed the revised manuscript. NM designed the data collection instruments, supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CASE REPORT
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Scurvy: A New Old Cause of Skeletal Pain in Young Children

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We report 3 cases of scurvy in children that occurred during a short period (2018) in a general pediatrics unit of a tertiary hospital for children in Paris. All children were around 3 years of age and were admitted for skeletal pain and altered general state, which mimicked infectious or malignant diseases. Their selective diet was not the prominent issue. The diagnosis of scurvy was delayed, after too many unnecessary examinations and medications. Bone imaging findings (X-ray and MRI) were *a posteriori* considered typical, but lesions were not easily identified as scurvy lesions because scurvy is not well-known by pediatricians and radiologists who should be mindful of this historical diagnosis.

Keywords: vitamin C, ascorbic acid, scurvy, selective diet, skeletal pain

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INTRODUCTION

Modern-day physicians tend to consider scurvy a disease of the past, first described in ancient times, as illustrated by the writings of Hippocrates (460 BC): "*… the breath smells bad, the gums separate from the teeth, blood runs from the nostrils, black-colored ulcerations frequently appear on the legs, some heal others do not, and the skin is thin…*". Similar descriptions are found in the writings of Jean de Joinville, a counselor to Louis IX of France, during the Seventh Crusade in Egypt in 1248–1254. More familiarly, the great navigators who underwent long expeditions (Vasco de Gama, 1497) suffered the first scurvy outbreaks. During the Renaissance, Jacques Henri Bernardin de St Pierre, aboard an East India Company ship in 1768, wrote: *"the first sign of scurvy is general lethargy: the patient craves rest; feels disgruntled; is sickened by everything; suffers during the day; only finds solace at night; then red dots appear on the legs and chest and bleeding ulcers appear on the gums. Frequently there are no outward signs at all, but the slightest cut remains incurable while we are at sea and progresses most rapidly. I sustained a slight cut to the end of my finger. Within 3 weeks the wound had ravaged the whole finger and had already spread to my hand despite all attempts to heal it. Several days after I had reached my destination it healed of its own accord."* In 1747, aboard the Salisbury, the surgeon James Lind undertook what is considered one of the first clinical trials: 12 patients with scurvy were administered different remedies, yet only those fed lemon or orange juice recovered (1–3). Francis Glisson first described scurvy in children in 1650, and found that it often occurred in addition to rickets. At the end of the nineteenth century, infantile scurvy resurged with the advent of heated milk and proprietary foods as popular infant foods, until Hess recommended that infants receiving heated milk should also receive fresh fruits. This recommendation led to the eradication of infantile scurvy in developed countries (4).

The present literature contains accounts of vitamin C deficiency in children in impoverished countries, notably a review published in Thailand in 2003 describing 28 children (mean age 29 months) with a diagnosis of scurvy, who had been fed a diet of ultra-high-temperature pasteurized

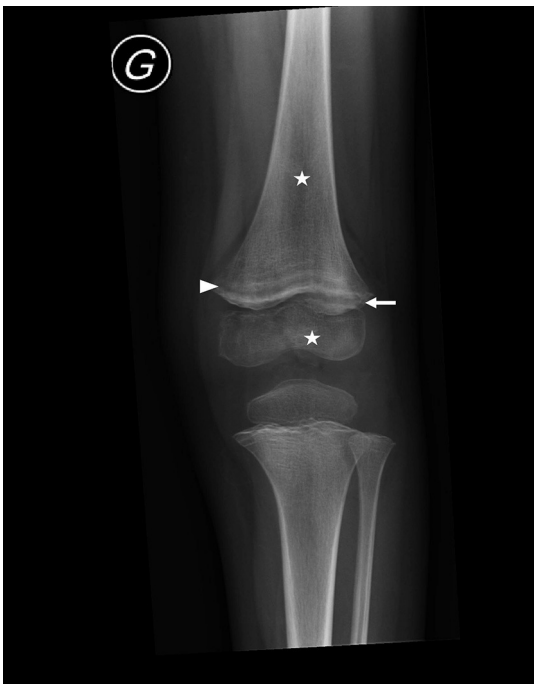

FIGURE 1 | Left knee radiograph for case I, a 3-year-old boy, demonstrating multiple clear metaphyseal bands in the distal femur (white arrowhead), also defined as "Trummerfeld zone," and marked white line corresponding to thickened zone of calcification, also named "white line of Frankel." Irregular and enlarged metaphyseal margin (white arrow), as well as diffuse osteopenia (stars) are also noted.

milk combined with cooked meat and starchy food but no fresh fruit or vegetables (5). The same year, a non-governmental organization reported a hemorrhagic fever epidemic in Afghanistan that in fact proved to be a scurvy outbreak (6). Despite this knowledge, a scurvy outbreak recently occurred in a refugee camp in Kenya in 2018 (7). In developed countries, scurvy is rare and mainly described in children with autism or neurological problems.

Here we present three cases that occurred during the same year, 2018, in children presenting to the general pediatrics unit of a tertiary hospital in a socially advantaged district of Paris, in children with no special needs.

CASE 1

A 3-year-old boy was admitted to the hospital for stunted growth, regression of walking, eating disorders and behavior troubles. He was exclusively breastfed for the first 12 months of his life, during which the transition to bottle-feeding with formula milk was unsuccessful. Therefore, breastfeeding was continued until 22 months of age, combined with an undiversified diet consisting of stewed fruits and dairy products. His initial psychomotor development was normal, but from 2 years of age, he became introverted and excessively irritable. His diet became more and more selective. During his third year of life, his growth rate had slowed. He sustained recurrent ear-nose-throat infections. One month before admission, his general condition had deteriorated; he was dejected and reluctant to walk, retreating into withdrawal behavior and playing somewhat repetitive games. After the boy was admitted to our department, we observed a malnourished and anxious child, refusing to walk. He ate only bread and goat's cheese. Clinical examination revealed conjunctival hyperemia involving bleeding from the lateral angle of the eye and erythematous gums that we attributed to an intercurrent viral infection. The initial suspected diagnosis was malignant disease and autism spectrum disorder. The septic workup was negative. Lower-limb radiographs revealed diffuse osteopenia associated with alternating dense and lucent metaphyseal bands and widening of the distal extremity of the femur (**Figure 1**).

In parallel, we searched for consequences of his selective diet but did not *a priori* think that all his symptoms could match scurvy. A nutritional assessment revealed low ferritin level (8 μg/L, $N = 15$–80) and null plasma vitamin C content. On this basis, classical scurvy involving gingivitis, conjunctival hemorrhage and bone damage was diagnosed but only 10 days after admission. Vitamin C treatment was rapidly effective. The boy regained motor function, and his general condition greatly improved. The diagnosis of autism spectrum disorder was ruled out.

CASE 2

A 3.5-year-old girl was admitted to hospital for pain on walking and persistent crying. She was the first child of healthy parents. Her appetite was low, yet growth was normal and her parents reported no restrictive eating behavior. Development was normal until 2 years of age, but for 6 months, she had been repeatedly complaining of leg pain and had intermittent limping that was attributed to transient synovitis or "growing pains." Two months before admission, the girl began to complain of left knee pain, and her appetite was suppressed, and she had become increasingly fatigued and irritable. Her diet had become increasingly selective, consisting of starchy food, dairy products and bread. We observed an introverted, anxious child who was prone to tears and easily distressed, especially when approached or touched. Objective assessment was normal in all other respects. Osteomyelitis was initially suspected despite no biological inflammatory reaction. She received an 8-day course of antibiotics. In light of persistent signs and a negative septic workup, leukemia was suspected. However, bone-marrow aspiration was normal. Initial radiograph findings showed mild vertebral osteopenia at T11, and MRI revealed symmetric bone-marrow signal changes in the metaphysis of long bones, more prominent in the lower extremities. These findings are compatible with malignancy, rheumatologic process such as chronic recurrent multifocal osteomyelitis or nutritional deficiency (**Figure 2**).

We suspected a chronic recurrent multifocal osteomyelitis and started anti-inflammatory treatment. During a staff meeting when the case was presented, the physician who had taken care

FIGURE 2 | Bilateral lower leg MRI for case 2, a 3.5-year-old girl: coronal fat-suppressed T2-weighted image revealing bilateral bone-marrow edematous changes of the metaphyseal area (white arrows) of the ankles and knees. Edematous changes were also noted in the distal epiphysis of the femur bilaterally (stars). Whole-body MRI shows multiple similar anomalies in the wrists and shoulders.

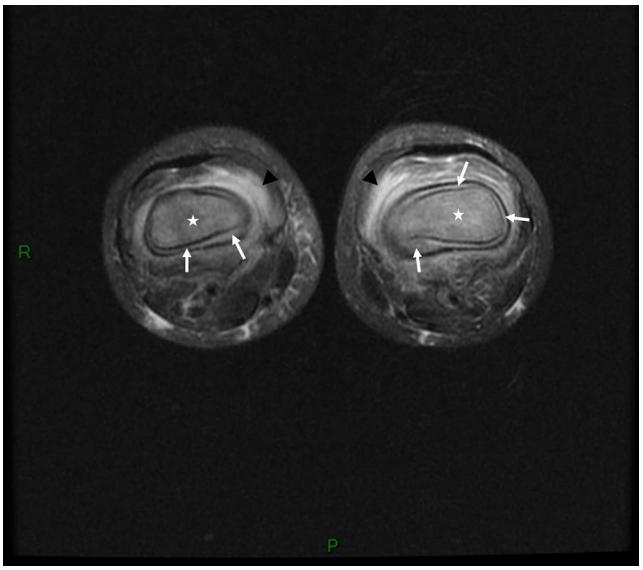

FIGURE 3 | Bilateral knee MRI for case 3, a 3-year-old girl: axial fat-suppressed T2-weighted image showing marked bilateral edematous bone-marrow changes within (stars) and around the bone (black arrowheads) associated with bilateral circumferential sub periosteal collections (white arrows) related to bilateral sub-periosteal hematomas.

of the first case described the above evoked scurvy. Plasma vitamin C content was severely deficient in the girl (0.8 μmol/L, normally 40–100 μmol/L) and confirmed scurvy but only 10 days after admission. Ferritin level was in the low range of standard (28 μg/l). Vitamin C treatment resulted in rapid reduction of all symptoms.

CASE 3

A 3-year-old girl was admitted to hospital for functional impairment in both lower limbs, with fever and deteriorated general physical condition. She was a twin, born at 34 weeks' gestation. Because of the parents' inadequate care, she and her sister were placed in foster care at birth, where they remained until age 7 months, when were returned to their family. Their development was satisfactory for the first year of life, but then the girl progressively developed an eating disorder, becoming selective. She would eat only a particular brand of creamy yogurt and a brand of mixed baby food. Although the quality of her diet was suboptimal, her quantity of intake seemed adequate, and she was growing well. At 8 days before admission, she was seen for lower-limb pain, fever and an inability to walk. Tests searching for infection yielded negative findings and the girl was discharged with a diagnosis of probable viral disease. The parents returned 3 days later because of persistent symptoms. The girl was admitted for evaluation. We observed an introverted, very unsociable and apprehensive girl, who lay flat in her stroller. She had dry skin and inflammatory hair follicles. Laboratory tests showed no inflammatory reaction. Bone radiographic findings were unremarkable; however, MRI of the lower limbs revealed multifocal symmetric bone-marrow signal anomalies within the metaphysis associated with circumferential sub-periosteal collections around both femoral metaphysis. Edematous signal changes were also noted in the deep and superficial tissues surrounding the elevated periosteum. These bone lesions immediately evoked scurvy (**Figure 3**). Plasma vitamin C content was severely deficient (0.4 μmol/L). Ferritin level was normal (66 μg/l). As noted in the previous cases, within days, vitamin C treatment had a positive effect on pain, behavior, and motor function.

COMMENTS

These 3 cases confirm that scurvy is a re-emerging disease that pediatricians need to consider, especially in the presence of unexplained bone pain, even in children with typical development. These three children, especially the child described in case 2, would have had fewer investigations if the diagnosis of scurvy had been considered earlier. Doctors must ask about dietary habits, especially in children around 3 years of age who are no longer receiving infant formula but who may not yet have a diversified diet.

Vitamin C or ascorbic acid is an essential vitamin since the occurrence of a genetic mutation inhibiting the conversion of glucose to ascorbic acid in primates 40 million years ago made humans dependent on an exogenous supply of vitamin C. This enzyme is still present in most mammals (8, 9). Vitamin C is very actively absorbed by the ileum and rapidly eliminated by

renal excretion. With excessive intake, it is absorbed passively and also excreted renally with no risk of overdose. However, insufficient intake owing to low reserves results in onset of biological deficiency within 3 months and clinical signs within 6 months (10). Ascorbic acid plays a critical role in the formation of type II collagen, and deficiency accounts for bone and vessel wall lesions. Ascorbic acid has antioxidant and anti-infection properties and enhances non-heme iron absorption and heavy metal detoxification (11).

Classical signs of scurvy include gingival lesions together with inflammation, hypertrophy and loosened teeth resulting from bleeding. Oral lesions accentuate anorexia, leading to food selectivity. Second-stage disorders are of a cutaneous nature, involving dry skin, folliculitis, vascular purpura and hematomas that can be painful, thus accentuating anorexia. Third-stage disorders are of a musculoskeletal nature, involving osteoporosis, bone growth abnormality, and subperiosteal or intraosseous hemorrhagic lesions that mimic inflammatory disease. Radiographic findings suggestive of scurvy are located in the metaphysis of all long bones, more prominent in the lower limb and include a clear metaphyseal band, also named "Trummerfeld zone;" marked white line corresponding to thickened zone of calcification also named "white line of Frankel;" irregular metaphyseal margin or metaphyseal fractures known as "Pelkan spur;" and diffuse osteopenia. MRI findings are concordant with radiographic findings: multifocal, symmetric bone-marrow changes in the metaphysis of long bones. When these features are associated with multifocal circumferential periosteum elevation, scurvy must be ruled out (12). Fourth-stage disorders affect the general physical condition, with asthenia and dejection that probably also perpetuate eating disorders. Of note, the symptoms leading to hospitalization in the 3 cases were skeletal symptoms.

The US recommended daily intake of vitamin C is 15 mg/day for children 1 to 3 years old, 25 mg/day for those 4 to 8 years old, approximately 50 mg/day for those 8 to 18 years old and 100 mg for adults. The richest food sources of vitamin C are fruit and vegetables, especially blackcurrants, parsley, peppers, lemons, lychees, strawberries, raspberries, gooseberries, papaya and kiwis (13).

In France, as in other developed countries, 3 sets of circumstances can lead to the re-emergence of scurvy. The first represents adults living in highly precarious conditions. The second is children whose selective diet is totally devoid of fresh fruit and vegetables. Such eating behaviors may occur in children with autism spectrum disorders or severe neurodevelopmental disabilities but also in children with aversion restrictive food intake disorders or only very selective eating behavior. Their diets must be totally devoid of fruits and vegetables, not only poor intake, as is commonplace. The third scenario is children fed a diet of vegetable beverage such as almond milk or other types of beverage popular with vegan parents. For these children, assessment of their nutritional status must be performed. Of note, in our cases, iron deficiency was present only in one out of three.

About 80 pediatric cases have been published in the past 20 years, essentially occurring in children with autism spectrum and neurodevelopmental disorders (14–23) but not necessarily (24–26). Vitamin C deficit is more frequent than classical scurvy, as recently shown by a retrospective review of the files of children with low ascorbic level (27). Further accounts are available on the Internet and in the general press.

CONCLUSION

Risk of scurvy continues to exist, even in developed countries, in individuals lacking vitamin C intake for more than 3 to 6 months. Therefore, caution is warranted for all children whose eating habits for whatever reason, are selective. For these selective-eating toddlers, in addition to psycho-educational rehabilitation, young children formula can be continued after 3 years of age, and vitamin C must be given as orange juice or vitamin supplements. Scurvy symptoms should be known to pediatricians. Similarly, pediatric radiologists should be mindful of scurvy, given that presentations frequently mimic infectious or malignant bone abnormalities.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CC, NV, HE, and SM are the pediatricians who cared for the children. NN and NB are the radiologists who helped us for the diagnosis of scurvy and selected the images. VA was the head of the general pediatric unit where the children were admitted. VA, CC, and HE wrote the manuscript. All the authors corrected the manuscript and validated the last version.

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OPINION
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Special Attention to Diet and Physical Activity in Children and Adolescents With Obesity During the Coronavirus Disease-2019 Pandemic

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Coronavirus disease 2019 (COVID-19) is an acute infectious respiratory disease that has posed critical challenges for the global healthcare community. Following the outbreak of COVID-19 (1), the Italian government imposed a national quarantine, restricting the movement of the population as a fundamental safety step to limit exposure to the virus and contain contagion. All schools were closed, requiring childcare and education to be provided at home; public spaces were also closed, and mobility was restricted to health or work situations. Unfortunately, the mandatory directives locking down outdoor activities inevitably disrupted the daily routine of children, including regular physical activity and excercise. This increased the risk of major weight gain for children already prone to gaining weight. Therefore, eating healthy foods and being physically active is recommended.

COVID-19 involves all age groups, although children are less likely to develop severe illness than adults (2). In adults, conditions such as chronic lung diseases, hypertension, cardiovascular disease, and diabetes, seem to increase the risk for an adverse COVID-19 outcome. The effect of obesity on the outcome remains controversial. Initially, such implications were not seriously considered; however, recent papers showed an association between obesity and severe outcome (3).

So far no reports on severity of disease in children with obesity compared to normal-weight subjects have been reported, that we know of. However, several studies show that obesity is associated with inflammation and severe airway obstruction in patients with respiratory tract infections (4). As reported by Okubo (5), pediatric obesity is an independent risk factor for severity and morbidity among children with lower respiratory tract infections by means of potential factors including subclinical inflammation, obesity-related immune system dysregulation, decreased cell-mediated immune responses, and obesity-related respiratory dysfunction (6). Adipose tissue expresses components of the renin-angiotensin system (RAS) (7), including the expression of angiotensin-converting enzyme 2 (ACE2–the functional receptor for SARS-CoV), which is up-regulated in the adipocytes of subjects with obesity, turning adipose tissue into a potential target and viral reservoir. Additionally, in high-fat-fed animal experimental models, researchers described dysregulated ACE2 expression as increasing the risk of COVID-19 infection (7).

Lockdowns may worsen not only the weight but also the eating habits of children, since homes are likely stocked with ultra-processed and calorie-dense comfort foods (8). Good nutrition is very important before, during, and after an infection. Although COVID-19 infection cannot be prevented by any food or dietary supplements, maintaining a healthy diet is an important part of supporting a strong immune system (4, 8).

TABLE 1 | Crucial advice for diet and physical activity in children and adolescents with obesity during the COVID-19 pandemic.

Eating habits and behaviors	Anti-inflammatory foods and hydration
DIET	
1. Sit down to family meals	1. Vegetables: *rich in Vitamin C (eg: citrus fruits, berries, bell peppers, broccoli, and sweet potatoes); rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach); rich in prebiotics*
2. Three meals and two snacks a day	2. Fruit: *rich in Vitamin C (eg: citrus fruits, berries, bell peppers, broccoli, and sweet potatoes); rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach); rich in prebiotics*
3. Varied diet (five food groups per meal)	3. Yogurt: *rich in probiotics*
4. Make half of your plate vegetables and fruits	4. Fish: *rich in omega 3*
5. Keep healthy food at hand	5. Nuts: *rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach)*
6. Prepare dishes in the kitchen together	6. Whole grains: *rich in prebiotics*
7. Correct portion sizes	7. Dried fruits and vegetables: *rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach); rich in prebiotics*
8. Teach children to make healthy desserts with fruit and yogurt	8. Beans: *rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach)*
9. Never use food as a reward	9. Olive oil: *rich in Poliphenols (eg: berries, apples, beans, nuts, artichokes, spinach)*
10. Give children some control	10. Water

Ranking	Name of the game	Ability	How to play	Duration	Frequency
PHYSICAL ACTIVITY					
1	Active breaks	Metabolism enhancement	Choose an exercise or a combination and do it non-stop	2–3 min	Every hour
2	Clean-up race	Agility and coordination	Set a timer or put on a song to see who can put the room to rights fastest, or clean the kitchen	Fastest!	Once a day
3	Play with pets	Aerobic training	Walk, run, jump, and play with balls with pets	20 min	Two or three times a day
4	Balloon games	Metabolism enhancement	Play with a balloon in a different way	30 min	Four times a week
5	Musical party	Aerobic training	Play music and dance or imitate "stars" on TV	30 min	Two times a week
6	Animal races	Coordination and resistance	Move like an animal (frog, crayfish, penguin, snake, etc.)	20 min	Four times a week
7	Obstacle course	Agility and coordination	Create an obstacle course with furniture in your apartment or outside.	30 min	Three times a week
8	Tape game	Coordination and resistance	Create shapes on the floor with tape and give instruction to complete a path.	30 min	Two times a week
9	Follow the leader	Metabolism enhancement	Focus on a sport, an activity, or an action. Imitate a person who has the leader role. Can also be played in video chat.	30 min	Two times a week
10	Exergames	Mixed	Play active videogames	An hour	Three times a week

1) Choose a few simple exercises: Walk on the spot, stretch arms and legs out to the side like a starfish while jumping, return arms to sides and legs to center on landing, circle arms, etc.

2) Parents' satisfaction: Children could help parents in the housework as an active play activity.

3) Play with pets: Walk or run in the house or outside, creating small paths.

4) Balloon games: Alone or with parents, children could throw the balloon at a wall, bounce it over their head, dribble it on a chair or table, hit it up in the air but do not let it touch the ground, place it between their knees and waddle across the room without dropping it.

5) Musical party: Sing and dance imitating a video on the internet.

6) Animal races: Children walk, hop, or crawl in the styles of various animals.

7) Obstacle course: Create an obstacle course with furniture in an apartment or outside. Some tools could be added: hula hoops to jump through, a line of tape to balance on, a table to crawl under, a blanket over two chairs to crab-walk through, etc.

8) Tape game: Parents use tape to lay a variety of shapes, letters, and/or numbers on the floor and prepare instructions to follow, e.g., "bear crawl to the square," "hop like a frog to the T," or "run to the rectangle."

9) Follow the leader: Stand face to face, about a foot apart, and have the child attempt to copy all your movements, reach up and stretch to the sky, do 10 jumping jacks, act like a monkey, etc.

10) Exergames: Use technology that uses interactive games to increase exercise behavior by requiring the players to physically interact with onscreen avatars through a variety of body movements while providing players the opportunity of being physically active and promoting their overall health.

Diet and nutrition play an important role in inflammation and immunity. Specific foods (8), including simple sugars, trans fats, refined carbohydrates, and processed meat, may promote inflammation and also counteract the anti-inflammatory effects of omega-3 fatty acids (9). Therefore, consumption of junk food may increase systemic inflammation in subjects with overweight or obesity, promoting IL-6 production (4).

Although inflammation is one of the body's first responses to infection, overactive immune responses in a persistent stress and inflammation condition may increase risk of severe infections.

Keeping children on a healthy diet in a safe home environment is an important strategy for maintaining weight control for children with obesity during this emergency coronavirus social lockdown, as is promoting physical activity (**Table 1**).

Children need to play and keep physically active to protect their physical and emotional health during growth (10). In particular, physical activity (PA) contributes to daily energy expenditure, thus increasing lean body mass, improving energy intake and metabolic and psychological profiles (10). A previous study by McManus et al. (11) on PA evaluation in normal weight and obese children showed no difference between children regarding moderate to vigorous PA, but further analysis showed that lack of light-intensity tasks in obese children explained the difference in total daily energy expenditure. Thus, in obese children, acquiring correct PA targets by means of frequent, short-duration day-to-day tasks, rather than sustained organized sport or exercise, is crucial. In fact, since obese children do not usually spend their leisure time in light-intensity activities, we believe that proper suggestions of games and active lifestyle habits will be crucial in confinement to small spaces. During the COVID-19 pandemic, PA or exercise restriction at school or in outdoor settings leads to a vicious cycle of sedentary behavior and decreased daily energy expenditure ending in weight gain. In light of this, the implementation of recreation and games as well as programmed PA at home becomes of primary importance.

In order to promote adherence to PA, we suggest different games (**Table 1**) that should be chosen according to the characteristics and personal preferences of the child. For each activity and game, recommendations are made for the duration and intensity necessary to gain muscular strength and flexibility, to improve fundamental motor skills and functions such as cardiorespiratory endurance, core stability, balance, and posture, and also to have fun.

Healthy diet and behaviors such as programmed physical activity, limited screen time, and adequate sleep may help children deal with these required social restriction rules, contributing to positive emotions, emotional stress responses, weight control, and health.

AUTHOR CONTRIBUTIONS

VC, MV, VP, and HC made a substantial contribution to the concept or design of the work, drafted the article, or revised it critically for important intellectual content. All authors approved the version to be published.

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BRIEF RESEARCH REPORT
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Mandatory Infant Vaccinations in France During the COVID-19 Pandemic in 2020

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Objectives: To describe changes in the dispensation of 11 mandatory vaccines to infants in France during the COVID-19 pandemic in 2020, considering the priming doses and boosters separately.

Methods: With data from the French national health database, all dispensations of priming doses and boosters of 11 mandatory vaccines [penta/hexavalent, measles mumps rubella (MMR), meningococcal conjugate type-C (Men-C-C), 13-valent pneumococcal conjugate (PCV13)] for infants ≤24 months old were aggregated by 4-week periods in 2020. Expected counts in 2020 were estimated according to counts in 2019 weighted by a ratio considering the level of vaccine dispensation before the pandemic onset in 2020. Relative differences (RDs) and their 95% confidence intervals (CIs) were computed to compare the observed and expected counts during the first and second lockdown and the period in between.

Results: During the first 4 weeks of the first lockdown, as compared with the expected numbers, the observed priming dose counts substantially decreased [RD: from −5.7% (95% CI −6.1; −5.2) for penta/hexavalent to −25.2% (95% CI −25.6; −24.8) for MMR], as did the booster counts [RD: from −15.3% (95% CI −15.9; −14.7) for penta/hexavalent to −20.7% (95% CI −21.3; −20.2) for Men-C-C]. Counts for priming doses and boosters remained slightly below the expected numbers after the lockdown. During 2020, MMR priming doses and the Men-C-C booster had the greatest shortfalls (N = 84,893 and 72,500, respectively).

Conclusions: This study provides evidence of a lack of vaccination catch-up after the first lockdown and a persistent shortfall in infant vaccination after the first 10 months of the COVID-19 pandemic in France, especially for the MMR priming doses and Men-C-C booster.

Keywords: COVID-19 pandemic, vaccination, infants (birth to 2 years), surveillance, national

INTRODUCTION

A mandatory immunization program is critical to protect infants against potentially life-threatening infections, and its schedule needs to be carefully respected (1), especially for the priming doses (2, 3). Experts consider that any delay in these priming doses is dangerous for the infant, whereas a delay of 1 or 2 months may be relativized for boosters (2, 4). The coronavirus disease (COVID-19) pandemic and its consequences have potentially disturbed this immunization program (5–8).

The COVID-19 pandemic was declared in France in February 2020 and has rapidly threatened the hospital system with saturation. France implemented its first national lockdown from March 17 to May 10, 2020, stopping non-essential economic and educational activities (9). This measure allowed for the attenuation of the first wave of the COVID-19 pandemic (10). With the acceleration of the second wave starting in August 2020, France implemented a curfew from October 17–30, 2020, then a second lockdown (October 30 to December 15), followed by a national curfew, which is ongoing. Although usual medical care access was maintained, parents may have been conflicted between the need to have their infant vaccinated and the fear that the infant might become infected by attending the practitioner's office (11).

Our aim was to describe the changes in the dispensation of 11 mandatory vaccines [measles, mumps, rubella (MMR), meningococcal conjugate type-C (Men-C-C), 13-valent pneumococcal conjugate (PCV13), and diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influenzae type b conjugate with or without hepatitis B combined in the hexavalent or pentavalent vaccine] (12, 13) among infants during the COVID-19 pandemic in France in 2020, considering the priming doses and boosters separately.

METHODS

In France, the infant immunization program is administered in primary care at ages 2, 4, and 11 months for the penta/hexavalent and PCV13 vaccines, 5 and 11 months for Men-C-C, and 12 and 16 months for MMR (13). Priming doses are defined as the first dose for Men-C-C and one of the first two doses for the other vaccines. The second dose for Men-C-C and the third dose for penta/hexavalent and PCV13 vaccines are the boosters. The MMR vaccine does not require a booster during infancy.

Analyses were conducted with data from the French National Health Data System, which contains all healthcare claims reimbursement data for 98.8% of the French population (14). The counts of reimbursed dispensations of each vaccine among infants $\leq$24 months old in 2020 were aggregated by 4-week periods. For each 4-week period from February 17 onward, expected counts in 2020 were estimated by weighting the number of dispensations observed in 2019 by the ratio of observed counts over weeks two to seven in 2020 to the corresponding counts in 2019. This process allowed for the consideration of the increasing trend of vaccine coverage between 2019 and 2020 before the onset of the pandemic in France (15). Relative differences (RDs) and their 95% confidence intervals (CIs) were computed to compare the observed and expected counts during the following periods: before (February 17–March 15) and during the first lockdown (March 16–May 10), then between the two lockdowns (May 11–October 29), and during the second lockdown (October 30–December 20). Every user of French public health insurance is informed of their right to oppose the use of their data for research purposes.

RESULTS

Evolution of Dispensed Priming Doses During the COVID-19 Pandemic

During the 4 weeks before the first lockdown, the number of priming dose dispensations was slightly below what was expected [penta/hexavalent: RD −1.3% (95% CI −1.9; −0.7); PCV13: −1.5% (95% CI −2.1; −0.9); Men-C-C: −1.7% (95% CI −2.5; −0.9); MMR: −6.5% (95% CI −7.1; −5.9); **Figure 1** and **Table 1**]. During the first 4 weeks of the lockdown, as compared with the expected numbers, the observed priming dose counts decreased by 12.4% (95% CI 11.9; 13.0) for penta/hexavalent, 12.6% (95% CI 12.0; 13.1) for PCV13, 21.0% (95% CI 20.3; 21.7) for Men-C-C, and 40.9% (95% CI 40.4; 41.3) for MMR. Then, the number of priming dose dispensations gradually increased during the second part of the lockdown, before slightly fluctuating below what was expected in the following 2 months. During the summer, counts were close to the expected numbers and slightly decreased again in September and October [penta/hexavalent: RD −5.4% (95% CI −5.8; −5.0); PCV13 −5.6% (95% CI −6.0; −5.2); Men-C-C: −3.7% (95% CI −4.2; −3.1); MMR −8.0% (95% CI −8.4; −7.6)]. Thus, during the 24 weeks after the first lockdown, the number of priming dose dispensations remained slightly lower than what was expected [penta/hexavalent: RD −3.4% (95% CI −3.6; −3.1); PCV13 −3.6% (95% CI −3.9; −3.4); Men-C-C: −1.3% (95% CI −1.7; −1.0); MMR −4.3% (95% CI −4.5; −4.1)].

During the 8 weeks of the second lockdown, the number of priming dose dispensations remained close to what was expected [penta/hexavalent: RD −2.9% (95% CI −3.3; −2.5); PCV13 −3.2% (95% CI −3.6; −2.8); Men-C-C: 1.1% (95% CI 0.5; 1.7); MMR: −1.5% (95% CI −1.9; −1.1)]. Overall, between March 16 and December 20, 2020, the number of priming dose dispensations was lower than what was expected for all vaccines, with shortfalls reaching 39,851 doses of penta/hexavalent [RD −3.7% (95% CI −3.9; −3.5)], 42,510 of PCV13 [−3.9% (95% CI −4.1; −3.8)], 15,393 of Men-C-C [−2.8% (95% CI −3.1; −2.5)], and 84,893 of MMR [−7.7% (95% CI −7.8; −7.5)]. Of note, ∼70% of the shortfalls for penta/hexavalent and PCV13 priming doses occurred after the first lockdown.

Evolution of Dispensed Boosters During the COVID-19 Pandemic

For boosters, in the 4 weeks before the first lockdown, the number of dispensations was slightly below what was expected [penta/hexavalent: RD −2.4% (95% CI −3.3; −1.5); PCV13: −1.7% (95% CI −2.6; −0.8); Men-C-C: −7.7% (95% CI

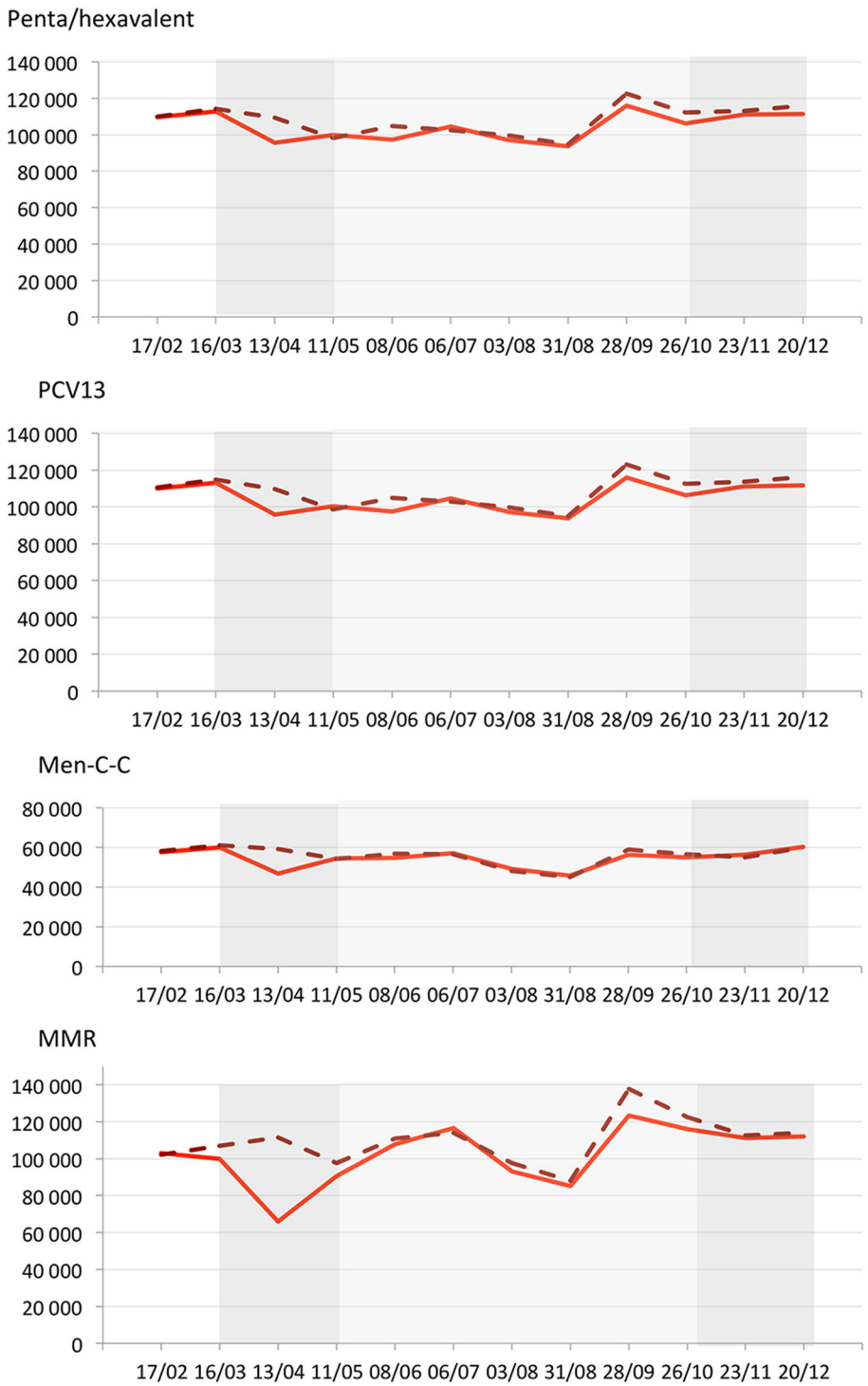

FIGURE 1 | Observed (solid red line) and expected (dashed red line) weekly counts for priming dose dispensations of penta/hexavalent, 13-valent-pneumococcal conjugate (PCV13), meningococcal-conjugate type-C (Men-C-C) and measles mumps rubella (MMR) in France (from January to December 2020). Dark gray rectangles illustrate the first and the second lockdowns (from 16/03 to 10/05 and from 30/10 to 15/12, respectively). Light gray rectangle illustrates the inter-lockdown period (11/05 to 29/10). The X-axis is in 4-week periods since the beginning of 2020. The Y axis represents the number of dispensed priming doses over the 4 previous weeks at each time point.

TABLE 1 | Relative differences between the observed and expected priming dose counts for penta/hexavalent, 13-valent pneumococcal conjugate (PCV13), meningococcal conjugate type C (Men-C-C), and measles mumps rubella (MMR) vaccines during the COVID-19 pandemic in France in 2020.

	Penta/hexavalent vaccine[a]			**PCV13 vaccine**			**Men-C-C vaccine**			**MMR vaccine**		
	Observed	**Expected**	**Relative difference**	**Observed**	**Expected**	**Relative difference**	**Observed**	**Expected**	**Relative difference**	**Observed**	**Expected**	**Relative difference**
	n	***n***	**% [95% CI]**	***n***	***n***	**% [95% CI]**	***n***	***n***	**% [95% CI]**	***n***	***n***	**% [95% CI]**
Pre-lockdown Feb 17-March 15	**112,716**	**114,213**	**−1.3 [−1.9; −0.7]**	**112,990**	**114,698**	**−1.5 [−2.1; −0.9]**	**60,113**	**61,138**	**−1.7 [−2.5; −0.9]**	**100,067**	**107,056**	**−6.5 [−7.1; −5.9]**
First lockdown	**195,636**	**207,387**	**−5.7 [−6.1; −5.2]**	**196,234**	**208,334**	**−5.8 [−6.2; −5.4]**	**101,234**	**113,622**	**−10.9 [−11.5; −10.4]**	**156,637**	**209,409**	**−25.2 [−25.6; −24.8]**
March 16-April 12	95,667	109,233	−12.4 [−13; −11,9]	95,904	109,706	−12.6 [−13.1; −12]	46,861	59,301	−21 [−21.7; −20.3]	65,969	111,613	−40.9 [−41.3; −40.4]
April 13-May 10	99,969	98,154	1.8 [1.2;2.5]	100,330	98,628	1.7 [1.1;2.4]	54,373	54,321	0.1 [−0.7;0.9]	90,668	97,796	−7.3 [−7.9; −6.7]
Inter-lockdown	**614,658**	**636,199**	**−3.4 [−3.6; −3.1]**	**615,340**	**638,407**	**−3.6 [−3.9; −3.4]**	**317,816**	**322,104**	**−1.3 [−1.7; −1]**	**642,213**	**671,009**	**−4.3 [−4.5; −4.1]**
May 11-June 7	97,379	104,694	−7 [−7.6; −6.4]	97,470	105,015	−7.2 [−7.8; −6.6]	54,696	56,787	−3.7 [−4.5; −2.9]	107,753	111,065	−3 [−3.6; −2.4]
June 8-July 5	104,431	102,558	1.8 [1.2;2.4]	104,495	102,984	1.5 [0.9;2.1]	57,081	56,690	0.7 [−0.1;1.5]	116,573	114,056	2.2 [1.6;2.8]
July 6-Aug 2	97,068	99,605	−2.5 [−3.2; −1.9]	97,131	99,798	−2.7 [−3.3; −2.1]	49,190	48,202	2.1 [1.2;3]	93.021	97,600	−4.7 [−5.3; −4.1]
Aug 3–30	93,697	94,623	−1 [−1.6; −0.3]	93,792	94,975	−1.2 [−1.9; −0.6]	45,707	45,059	1.4 [0.5;2.4]	85,327	87,904	−2.9 [−3.6; −2.3]
Aug 31-Sept 27	115,914	122,602	−5.5 [−6; −4.9]	116,063	122,996	−5.6 [−6.2; −5.1]	56,264	58,878	−4.4 [−5.2; −3.6]	123,470	137,823	−10.4 [−10.9; −9.9]
Sept 28-Oct 25	106,169	112,117	−5.3 [−5.9; −4.7]	106,389	112,639	−5.5 [−6.1; −5]	54,878	56,488	−2.8 [−3.7; −2]	116,069	122,561	−5.3 [−5.8; −4.8]
Second lockdown	**222,409**	**228,968**	**−2.9 [−3.3; −2.5]**	**222,745**	**230,088**	**−3.2 [−3.6; −2.8]**	**116,474**	**115,191**	**1.1 [0.5;1.7]**	**223,193**	**226,520**	**−1.5 [−1.9; −1.1]**
Oct 26-Nov 23	110,950	113,126	−1.9 [−2.5; −1.3]	110,996	113,754	−2.4 [−3; −1.8]	56,321	55,058	2.3 [1.5;3.1]	111,199	112,530	−1.2 [−1.8; −0.6]
Nov 24-Dec 20	111,459	115,842	−3.8 [−4.3; −3.2]	111,749	116,334	−3.9 [−4.5; −3.4]	60,153	60,133	0 [−0.8;0.8]	111,994	113,990	−1.8 [−2.3; −1.2]
Since first lockdown March16-Dec 20	**1,032,703**	**1,072,554**	**−3.7 [−3.9; −3.5]**	**1,034,319**	**1,076,829**	**−3.9 [−4.1; −3.8]**	**535,524**	**550,917**	**−2.8 [−3.1; −2.5]**	**1,022,043**	**1,106,936**	**−7.7 [−7.8; −7.5]**

[a] *Pentavalent and hexavalent vaccines combine vaccines for diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influenzae type b conjugate without or with hepatitis B, respectively.*
CI, confidence interval.

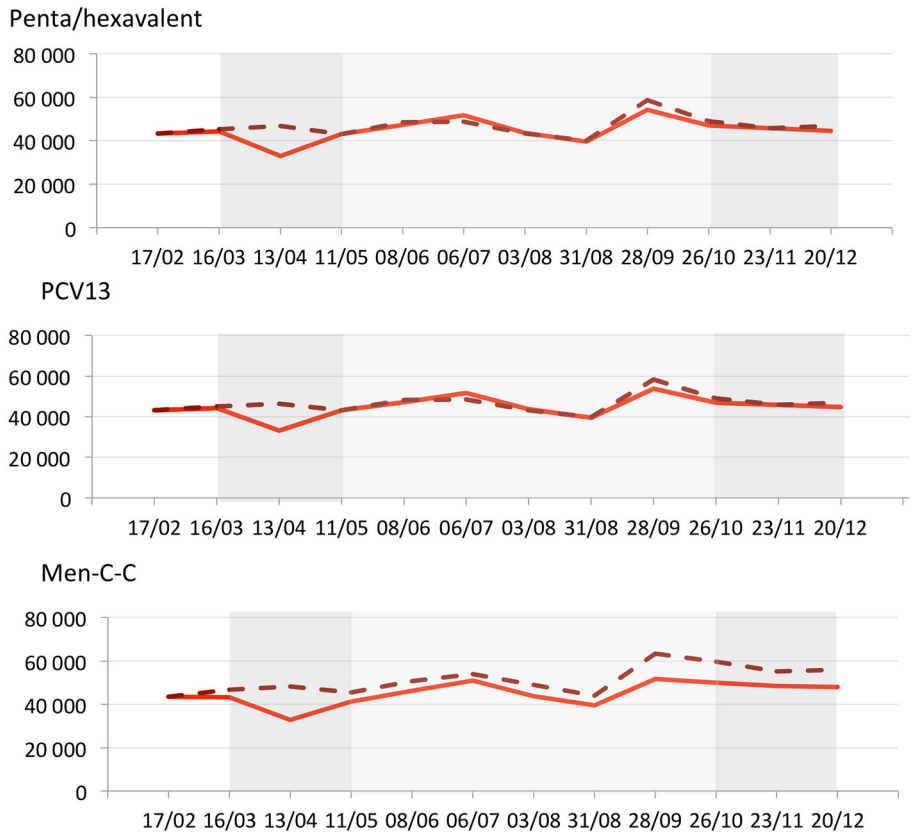

FIGURE 2 | Observed (solid red line) and expected (dashed red line) weekly counts for booster dispensations of penta/hexavalent, 13-valent-pneumococcal conjugate (PCV13), meningococcal-conjugate type-C (Men-C-C) and measles mumps rubella (MMR) in France (from January 20 to December 20, 2020). Dark gray rectangles illustrate the first and the second lockdowns (from 16/03 to 10/05 and from 30/10 to 15/12, respectively). Light gray rectangle illustrates the inter-lockdown period (11/05 to 29/10). The X-axis is in 4-week periods since the beginning of 2020. The Y axis represents the number of dispensed boosters over the 4 previous weeks at each time point.

−8.5; −6.8); **Figure 2** and **Table 2**]. During the first 4 weeks of the lockdown, as compared with the expected numbers, observed booster counts decreased by 29.4% (95% CI 28.6; 30.2) for penta/hexavalent, 28.7% (95% CI 28.0; 29.5) for PCV13, and 31.9% (95% CI 31.2; 32.7) for Men-C-C. Then, the number of booster dispensations returned to levels close to those expected for all boosters. During the 24 weeks after the first lockdown, booster dispensations remained slightly below those expected for penta/hexavalent and PCV13 [RD −1.7% (95% CI −2.1; −1.4) and −1.5% (95% CI −1.9; −1.1), respectively] but substantially reduced for Men-C-C [RD −11.9% (95% CI −12.2; −11.6)]. During the 8 weeks of the second lockdown, the number of booster dispensations was similarly reduced [penta/hexavalent: RD −2.6% (95% CI −3.2; −1.9); PCV13 −2.3% (95% CI −3.0; −1.7); Men-C-C: −13.4% (95% CI −13.9; −12.9)]. Overall, the number of booster dispensations between March 16 and December 20, 2020 was lower than what was expected for all vaccines, with shortfalls reaching 21,140 doses of penta/hexavalent [RD −4.5% (95% CI −4.8; −4.2)], 19,700 of PCV13 [−4.2% (95% CI −4.5; −3.9)], and 72,500 of Men-C-C [−13.8% (95% CI −14.1; −13.5)].

DISCUSSION

During the first 10 months of the COVID-19 pandemic in 2020 in France, all mandatory priming dose and booster dispensations were reduced as compared with the expected estimates based on the previous year. The reduction was particularly striking during the first 4 weeks of the first lockdown, especially for the MMR priming doses and the Men-C-C booster. Since August 2020, the second wave of the pandemic was associated with a slight continual deficit in vaccine dispensations affecting the priming doses and boosters in similar proportions, and these trends were not substantially affected by the second lockdown.

Early decreases in infant vaccination uptake in France during the first lockdown appear to be less marked than in the United States (6–8) but higher than in the United Kingdom (5), where routine vaccinations are not mandatory. After the first month of the lockdown, the shortfall attenuated somewhat faster than in the United States (6–8). French authorities' messages promoting infant vaccination, which were widely disseminated from the third week of the lockdown, may have contributed to this (16–18). As in the United States, (6–8) our study in France reveals that during the first lockdown, the decrease was somewhat

TABLE 2 | Relative differences between the observed and expected booster counts for penta/hexavalent, 13-valent pneumococcal conjugate (PCV13), and meningococcal conjugate type-C (Men-C-C) vaccines during the COVID-19 pandemic in France in 2020.

	Penta/hexavalent vaccine[a]			PCV13 vaccine			Men-C-C vaccine		
	Observed	**Expected**	**Relative difference**	**Observed**	**Expected**	**Relative difference**	**Observed**	**Expected**	**Relative difference**
Pre-lockdown Feb 17–March 15	**44,174**	**45,262**	**−2.4 [−3.3; −1.5]**	**44,218**	**44,996**	**−1.7 [−2.6; −0.8]**	**43,218**	**46,813**	**−7.7 [−8.5; −6.8]**
First lockdown	**76,037**	**89,782**	**−15.3 [−15.9; −14.7]**	**76,278**	**89,536**	**−14.8 [−15.4; −14.2]**	**74,164**	**93,552**	**−20.7 [−21.3; −20.2]**
March 16-April 12	32,945	46,666	−29.4 [−30.2; −28.6]	33,123	46,472	−28.7 [−29.5; −28]	32,776	48,152	−31.9 [−32.7; −31.2]
April 13-May 10	43,092	43,116	−0.1 [−1;0.9]	43,155	43,064	0.2 [−0.7;1.2]	41,388	45,400	−8.8 [−9.7; −8]
Inter-lockdown	**283,135**	**288,153**	**−1.7 [−2.1; −1.4]**	**282,693**	**286,971**	**−1.5 [−1.9; −1.1]**	**282,285**	**320,478**	**−11.9 [−12.2; −11.6]**
May 11-June 7	47,149	48,541	−2.9 [−3.7; −2]	47,164	48,295	−2.3 [−3.2; −1.5]	46,254	50,640	−8.7 [−9.5; −7.8]
June 8-July 5	51,618	48,661	6.1 [5.2;7]	51,630	48,463	6.5 [5.6;7.5]	50,885	53,871	−5.5 [−6.4; −4.7]
July 6-Aug 2	43,575	43,243	0.8 [−0.2;1.7]	43,618	43,104	1.2 [0.2;2.1]	43,872	48,945	−10.4 [−11.2; −9.5]
Aug 3–30	39,593	40,013	−1.1 [−2; −0.1]	39,499	39,744	−0.6 [−1.6;0.4]	39,598	44,047	−10.1 [−11; −9.2]
Aug 31-Sept 27	54,194	58,673	−7.6 [−8.4; −6.9]	53,874	58,382	−7.7 [−8.5; −6.9]	51,826	63,328	−18.2 [−18.9; −17.5]
Sept 28-Oct 25	47,006	49,022	−4.1 [−5; −3.2]	46,908	48,983	−4.2 [−5.1; −3.4]	49,850	59,647	−16.4 [−17.2; −15.7]
Second lockdown	**90,212**	**92,589**	**−2.6 [−3.2; −1.9]**	**90,453**	**92,617**	**−2.3 [−3; −1.7]**	**96,386**	**111,305**	**−13.4 [−13.9; −12.9]**
Oct 26-Nov 23	45,690	45,777	−0.2 [−1.1;0.7]	45,779	45,734	0.1 [−0.8;1]	48,358	55,255	−12.5 [−13.3; −11.7]
Nov 24-Dec 20	44,522	46,812	−4.9 [−5.8; −4]	44,674	46,883	−4.7 [−5.6; −3.8]	48,028	56,050	−14.3 [−15.1; −13.5]
Since first lockdown March 16-Dec 20	**449,384**	**470,524**	**−4.5 [−4.8; −4.2]**	**449,424**	**469,124**	**−4.2 [−4.5; −3.9]**	**452,835**	**525,335**	**−13.8 [−14.1; −13.5]**

[a] *Pentavalent and hexavalent vaccines combine vaccines for diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influenzae type b conjugate without or with hepatitis B, respectively.*

less prominent for the priming doses usually administered before 5 months of age (penta/hexavalent, PCV-13, Men-C-C priming doses) than for boosters and MMR, which are administered at an older age.

During the immediate post-lockdown period, the counts for all mandatory vaccine dispensations remained slightly below what was expected. In August 2020, no clear trend toward a catch-up had occurred. Since the onset of the second wave, vaccine dispensations have been declining again. This second deficit differed from the pattern during the first wave: priming doses and boosters were slightly and persistently affected in similar proportions (about 4%).

During the first 10 months of the COVID-19 pandemic, vaccines with suboptimal coverage in the previous years, namely the Men-C-C booster and MMR priming dose, were more affected than the others (15). For these two vaccines, the cumulative shortfalls reached more than 70,000 doses since the pandemic onset. Also, for the penta/hexavalent and PCV13 priming doses, 70% of the cumulative shortfalls occurred after the first lockdown. From a Delphi survey, experts considered that a delay >15 days for most of the priming doses and a delay >2 months for the MMR priming dose and boosters after the recommended age are potentially dangerous for infants (2).

The chronic vaccine deficit might also cause new outbreaks of vaccine-preventable diseases. Following the mandatory Men-C-C vaccination, the coverage of the Men-C-C first dose increased from 39% in 2017 to 76% in 2018 (15) and led to a decrease in invasive meningococcal C infections in 2019 (invasive meningococcal C infection incidence was 0.1/100,000 inhabitants in France in 2019) (19). However, the waning immunity due to the deficit of Men-C-C booster at 12 months of age may put infants who did not receive the booster at risk of invasive meningococcal C infection after 1 year of age (20). For the MMR vaccine, the first dose coverage at 12 months of age increased by only 3.3 points in France between 2016 and 2018 (from 74.3 to 77.7%) (15). Given the insufficient vaccine coverage of the overall population, measles outbreaks were observed in recent years in the United States and in several European countries including France (the measles incidence was 4/100,000 inhabitants in 2019) (21–23). Although barrier measures and the two lockdowns slowed the overall outbreaks of respiratory diseases, the MMR vaccine deficit observed in 2020 might favor new measles outbreaks after the COVID-19 pandemic. Recently, resurgences of pertussis were noted among the youngest children in the United States and several European countries despite a high vaccine coverage (24). Several hypotheses are under consideration to explain these resurgences, such as an earlier waning of protective immunity of the pertussis acellular vaccine and the circulation of *Bordetella* pertussis variants with depletion of vaccine-included antigens (24). In this context, the prolonged vaccination deficit, albeit slight, might promote new pertussis outbreaks.

The vaccine shortfall may be explained by parental concerns about potentially exposing their children to COVID-19 during the immunization visit (5, 6). Parental knowledge about the benefits of the first vaccinations for their infants may have mitigated their fears and limited the decrease in delivery of these priming doses during the first month of the pandemic. Beyond the fear of COVID-19, vaccination delay or refusal may be related to vaccine hesitancy (25), especially in France, with the strongest negative sentiment related to vaccine safety in the world (26). A systematic review showed that barriers to vaccination access were persistent among children from families of low socioeconomic status (27). Risk factors for vaccination shortfalls, especially socio-economic and geographic factors, need to be explored to identify infants at risk of vaccine delay.

This study has substantial strengths. It is based on a comprehensive national database from a country with ∼1,400,000 infants born per year (28). To better assess the potential influence of the pandemic and its consequences on vaccine dispensations, the expected counts were calculated considering the increasing trend of vaccine coverage (15) in early 2020 as compared with 2019. We separately investigated the priming dose and boosters because a delay in the priming doses is more dangerous than for the boosters.

The main limitation of this study is that the evolution of dispensed vaccinations does not precisely provide information on the status of vaccine coverage in France. These dispensation data may have underestimated the deficit of actually injected vaccines during the pandemic because parents may have obtained the vaccine at the pharmacy but not visited the practitioner for injection for fear of exposing their child to COVID-19 (11). Finally, the administrative nature of the data does not provide information on the causes of the lack of vaccine catch-up and the chronic lack of vaccine dispensations.

CONCLUSION

This study provides evidence of a persistent shortfall in infant vaccination during the first 10 months of the COVID-19 pandemic in France, especially for the MMR priming doses and Men-C-C booster. The increasing trend of vaccine coverage observed since 2018 (15) has been weakened as a consequence of the pandemic in France. Vaccination should be closely monitored and strongly encouraged using all available media to safeguard children against future outbreaks.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the procedures carried out with the French data privacy authority (CNIL, Commission nationale de l'informatique et des libertés) do not provide for the transmission of the database. All requests for access must be submitted to the Health data hub. Requests to access the datasets should be directed to these websites: https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees—https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html#les-acces-sur-projet.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required

to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AW, RD-S, MZ, and MT conceptualized and designed the study. JD and LO designed the data collection instruments, collected data, and carried out the initial analyses. MT supervised data collection and drafted the initial manuscript. AW, RD-S, MZ, JD, LO, and JT critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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BRIEF RESEARCH REPORT
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Face Masks in Young Children During the COVID-19 Pandemic: Parents' and Pediatricians' Point of View

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Background: In countries with high SARS-CoV-2 circulation, the pandemic has presented many challenges on different fronts, affecting lives and livelihoods; efforts to keep schools open are among the most important. In France, to keep schools open, wearing a face mask has been mandatory for children from age 6 years since November 2020.

Objective: To evaluate the acceptability and tolerance of this measure by children as well as both parents and pediatricians.

Setting: Parents registered on the website of the French Association of Ambulatory Pediatrics and pediatricians members of this association.

Participants: All parents and pediatricians who agreed to take part in the survey.

Results: Among the 2,954 questionnaires for the parents' survey, the reasons for wearing a mask were understood by 54.6% of parents, most of whom (84.6%) explained the reasons to their children. The parents applied this measure because it was mandatory (93.4%) even if they disagreed (63.3%). When interviewed by parents, children said they were usually embarrassed (80.9%) by the mask. The main symptoms or changes of behavior attributed to the mask according to parents were headache (49.0%), speaking difficulties (45%), change in mood (45.2%) and breathing discomfort (28.1%). Among the 663 pediatricians who responded, many agreed with mandatory mask-wearing at age 6 years (67.7%). Overall, 15% of pediatricians systematically asked about the mask tolerance during the consultation. During the medical consultation, when the parents complained about the mask (64.3%), the main drawbacks were related to fog on glasses (reported by 68.2% of pediatricians), breathing discomfort (53.1% of pediatricians), cutaneous disorders (42.4% of pediatricians) and headaches (38.2% of pediatricians).

Conclusion: Despite the many inconveniences reported, children agree to wear the mask better than their parents think. Pediatricians should sufficiently take the opportunity during the consultation to further explain the reasons for wearing the mask because their pedagogical role is crucial.

Keywords: face mask, pandemic, COVID-19, children, parenthood

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INTRODUCTION

COVID-19 is an extremely contagious viral disease, with essentially respiratory tropism, due to the SARS-CoV-2 virus. Since December 2019, this virus was responsible for a pandemic that reached more than 100 million people and caused 2.3 million deaths worldwide as of February 2021[1]. Children are less often affected than adults and have exceptionally severe illness (1–4). At the beginning of the pandemic, the disease was assumed to be transmitted mainly via children, as observed during influenza epidemics; school closures proved effective in limiting the spread of the disease (5). By analogy with the flu, to protect children and fight against the spread of COVID-19, as part of the lockdown, many countries made the drastic decision to close schools and universities[2]. Thus, at the end of March 2020, 166 countries had implemented this measure, depriving 1.5 billion schoolchildren and students of education[2].

However, the effectiveness of this radical school closure measure to fight the pandemic and decrease the risk of contamination of adults working at schools has not yet been demonstrated (6–8). Conversely, the fight against the pandemic has been effective in some countries such as Taiwan, which did not implement widespread school closures (9). In a recent French study, more than 80% of children with positive SARS-CoV-2 results by RT-PCR or serology had a confirmed or suspected COVID-19 household contact (10). Indeed, the most frequent source of contamination of children is not the school but rather the family and home environment (11, 12). Nevertheless, the contamination at school exists but is minor (13, 14). Moreover, the prolonged closure of schools has resulted in adverse consequences for both children and their parents who work from home (15, 16). All of these drawbacks were even greater in low-income families (17). In this context, France made many efforts to keep schools open even with high viral circulation[3]. Until high COVID-19 vaccination coverage is reached with a vaccinated population of all ages, other effective measures should be implemented to limit the spread of the epidemic among children who are often asymptomatic carriers.

Among these measures to limit the spread, maintaining a distance of more than 1 m as long as possible, frequent hand washing, and wearing a face mask have shown their effectiveness (18, 19). Medical or surgical masks help protect people around children and offer some protection to children. The FFP2 (N95) masks that filter 94% of the particles prevents the transmission of the virus from the patient to caregivers but is not suitable for children, except in special cases (e.g., cystic fibrosis or severely immunocompromised children). The visor is useful only if it is used in addition to a mask; it is rarely used by children[4].

Therefore, in France, to keep schools open, wearing a face mask has been mandatory in middle school since September 2020[5]. During the second lockdown, on November 2, 2020, this requirement was extended to children from age 6 years[5].

In this context, we surveyed both parents and pediatricians to evaluate the acceptability and tolerance of mask-wearing in young children.

METHODS

The French Association of Ambulatory Pediatrics (AFPA) administered two surveys via their websites (www.mpedia.fr and https://afpa.org/). The two different anonymous questionnaires with closed questions (**Supplementary Material**) were available online; one was targeted to parents, the other to pediatricians. The data were collected by using SurveyMonkey (SurveyMonkey Inc.).

Survey Targeted to The Parents

A first group of questions focused on the understanding and acceptance of mask-wearing by parents and children. A second group of questions asked about side-effects possibly attributed to the mask, with a list provided. The last questions asked about the socio-economic profile of the family.

Several e-mails with a link to the SurveyMonkey questionnaire were sent to the 10,000 subscribers of the mpedia.fr site in December 2020 and to different social networks. Parents were asked to answer only if they had a child attending primary school, regardless of age. If there were several siblings, the parents had to answer for the youngest child only.

Survey Targeted to The Pediatricians

The questions first focused on the demographic characteristics of the pediatrician, followed by their point of view regarding the mandatory requirement for children to wear a face mask. Another group of questions asked about discussions regarding mask-wearing and its possible side-effects between the pediatrician, the child and the parents during a consultation. The last group of questions asked about how the pediatrician could convince both parents and children of the benefits of mask-wearing. Three successive emails with a link to the SurveyMonkey questionnaire were sent to the 1,613 AFPA subscribers in December 2020.

Our data being strictly anonymous, no ethics committee approval was requested for this study.

Statistical Analysis

Our sample of responding parents included a high number with high socio-professional categories as compared with the 2016 National Perinatal Survey (NPS) study, which is a representative reference of the population of parents of young children

[1]Available online at: https://www.statista.com/statistics/1093256/novel-coronavirus-2019ncov-deaths-worldwide-by-country/ (accessed February 11, 2021).

[2]Available online at: https://en.unesco.org/covid19/educationresponse (accessed February 11, 2021).

[3]Available online at: https://afpa.org/content/uploads/2021/01/Position-de-la-SFP-AFPA-25-janvier-2021-002.pdf (accessed February 11, 2021).

[4]Available online at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover-guidance.html (2019).

[5]Available online at: https://www.legifrance.gouv.fr/loda/id/JORFTEXT000042475143/2020-11-03/ (accessed February 11, 2021).

living in metropolitan France. For better representativeness, the results of the parent survey were adjusted according to socio-professional situation of the NPS study (20). An adapted coefficient was applied to the parents' responses according to the under/over-represented occupations. This coefficient was defined by the relative frequency of occupation categories according to the parents' survey and the 2016 NPS baseline data. Thus, regarding socio-professional categories, the results obtained can be considered representative of the population of parents with young children living in France. In the absence of a response for the father's occupation, the mother's occupation was used. If the parents' occupation was not given, the questionnaire was not considered.

Responses (frequency and percentage) were analyzed by using Stata/SE v15 (StataCorp, College Station, TX, USA). Chi-square test was used for inter-group comparisons, and $p < 0.05$ was considered statistically significant.

RESULTS

Survey Targeted to Parents

Among the 2,954 analyzed questionnaires, the age of the children for whom parents responded was distributed as follows: <6 years (25.7%), 6 years (6%), 7 years (23.9%), 8 years (17.4%), 9 years (10.7%), 10 years (6.8%), and ≥11 years (9.5%). Most of the responses were given by mothers (89.2%) from 30 to 39 years old (54.2%) with often a bachelor's degree (74.5%). All regions in France were represented, with the least responses from Corsica (0.2% of responses) and the most from Auvergne-Rhône-Alpes (17.5% of responses).

Understanding and Acceptance of The Mask by Parents and Children

Slightly more than half of the parents (54.6%) said they understood the reasons for wearing a mask; most (84.6%) explained the reasons to their children. Most often, the parents applied this measure because it was mandatory (93.4%) even if they disagreed (63.3%) or were unable to know if it was useful (13.7%). In total, 76.2% of parents stated that their children understood the reasons for wearing a mask, and for many (59.7%), the children had become accustomed to wearing it. Children interviewed by their parents said they were usually embarrassed (80.9%) by the mask. Outside of school, 24.8% of children continued to wear the mask even if it was not mandatory. Globally, according to parents' declarations, accepting the mask was more difficult for children aged 10 years than 6 years (50.8 vs. 23.9%, $p < 0.001$), as was understanding the reasons for wearing it (29.2 vs. 14.7%, $p = 0.002$).

Potential Side-Effects of Face-Masking

Since wearing the mask became a requirement, parents reported several side-effects in children: 82.4% presented different physical symptoms and 67.0% behavioral changes (**Figure 1**). The main symptoms attributed to the mask by the parents were headache (49.0%) followed by speaking difficulties (45.1%) and breathing discomfort (28.1%). The main changes in behavior reported by the parents were change in mood (45.2%).

When parents or children did not understand the reasons for wearing the mask, child tolerance was reduced, symptoms and behavioral changes were twice as frequent (except fogged glasses), and the number of children who were used to the mask was reduced.

Survey Targeted to The Pediatrician

Among the 663 pediatricians who replied to the questionnaire, 83.6% were women; 24.7% were <40 years old and 28.0% were >61 years old. All France regions were represented, with the least responses from Corsica (0.5% of responses) and the most from the Paris area (23.0% of responses).

Pediatricians' Point of View and Discussion With Parents and Children Regarding Mandatory Masks

Many pediatricians agreed with mandatory mask-wearing from age 6 years (67.7%). During the pediatrician consultation, the question of the mask was spontaneously addressed by the parents and/or children (80.9% of pediatricians), and 15.0% of pediatricians systematically asked the question about mask tolerance. According to 23.5% of pediatricians, parents came for a specific visit due to symptoms attributed to the mask. For 64.3% of pediatricians, the parents complained about their child wearing a mask. The main drawbacks were related to fog on glasses (reported by 68.2% of pediatricians), breathing discomfort (53.1% of pediatricians), cutaneous disorders (42.4% of pediatricians) and headaches (38.2% of pediatricians).

The Convincing Power of The Pediatrician

More than one third of pediatricians (37.1%) reported that a few parents tried to obtain a certificate to justify that their child could not wear the mask, but more than half of these pediatricians (55.7%) convinced the parents. When the reasons for exemption from wearing a mask were justified (33.8% of pediatricians), it was most often for neurodevelopmental disorders (72.3%) and less often for asthma (25.8%).

DISCUSSION

This study combines the views of pediatricians, parents and therefore their children on the important issue of mask-wearing from age 6 years. Many pediatricians agreed with mandatory mask-wearing from age 6 years (67.7%), but many parents disagreed (63.3%). By contrast to young adults, children in our study agreed to wear the mask with good acceptability (21), and for 59.7% of parents, their children had become accustomed to wearing it. Because they have a significant educational role, pediatricians should take the opportunity during the consultation to further explain the reasons for wearing the mask.

Surprisingly, according to the parents' declarations, children aged 10 years had more difficulties accepting the mask and understanding the reasons for wearing it than children aged 6 years. This result suggests that parents or teachers took more time to explain the recommendations and the reasons to the youngest

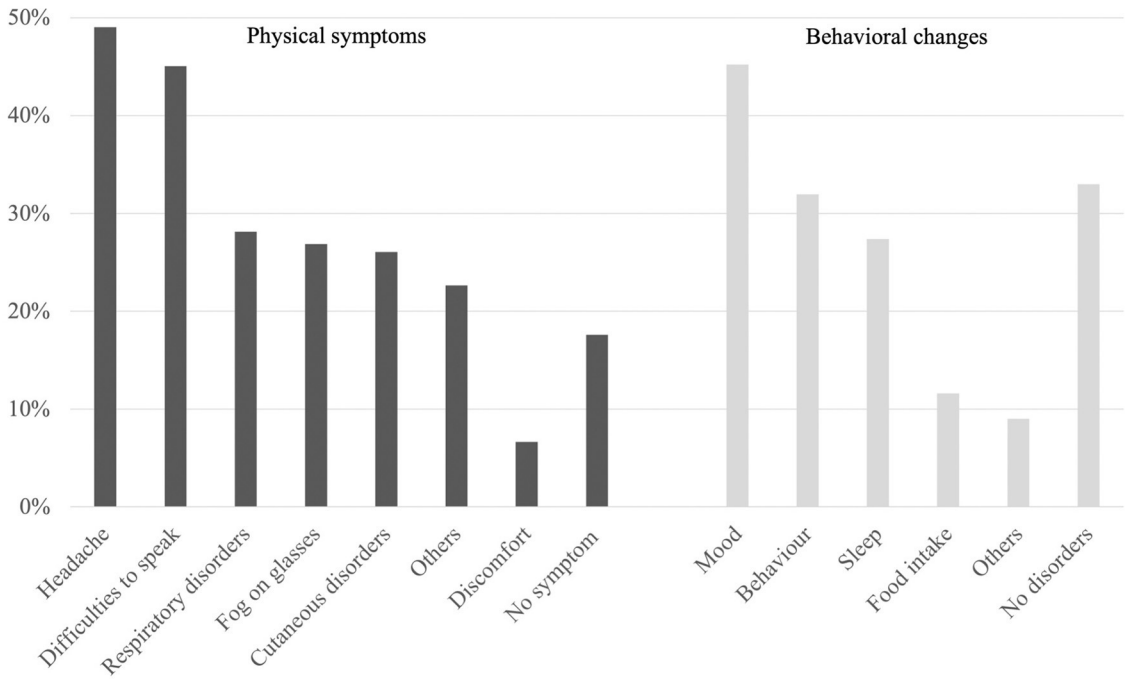

FIGURE 1 | Physical symptoms and behavioral changes attributed to mask-wearing (parents' survey).

TABLE 1 | Advice for parents/children, teachers and pediatricians to promote and accept wearing a mask [from (34)].

Recommendations to parents
Masks are made to protect children and their loved ones
Mask-wearing is a reflex, such as seat belt in a car and helmet on a bicycle
Fit the mask to the child's size
Let the child choose the mask she/he likes
Always have a mask available
Take your time to explain mask-wearing with age-appropriate words
Have the child put on a mask at home, with the parents, to get used to it
Put a mask on a stuffed animal
Parents should be aware of how facial masks can harm the intensity and quality of speech and how much this can affect the school performance of their child
Be aware of the child's daily school performance
Talk to the child about the day at school and about the difficulties he/she may have
Observe behavior changes that may indicate school difficulties
Recommendations to teachers
Speak slowly and articulate speech
Use features and visual support and images in activities
Reduce environmental noise and keep the child's attention before speaking
Consider using a portable microphone
Ask the child to repeat the instructions received, making sure that the child has really understood
Repeat the instructions or rephrase your speech if the child is not understanding what is being requested
Do not speak loudly; do not overemphasize, or exaggerate your words
Do not talk to the child while walking; always make eye contact
Avoid using flashy masks because they can compete for the child's attention, dispersing the listener's focus
Recommendations to pediatricians
Take advantage of each consultation for talking about the mask and the pandemic, for explaining and detecting side effects or behavioral changes, and for reassuring

children. Another possibility is that at age 10, children start to be in pre-adolescence and object to instructions.

According to the parents' and pediatricians' survey, complaints about mask-wearing were common. Indeed, the symptoms attributed to the mask were frequent (82.4%), and headache was reported for almost half of the children. Unfortunately, our questionnaire did not ask whether children previously had headache. Although the prevalence of headache appeared high, it was comparable to that found in children before the pandemic: 37–51% in children >7 years old (22). A similar prevalence of headache (50%) was found in nurses equipped with an FFP2 mask (23). The mechanisms evoked were often multifactorial: mechanical factors, hypoxia, hypercapnia, and stress (24). Another complaint was the children's discomfort in speaking, reported by 45% of parents. This result was not surprising because obviously the mask is a hindrance to elocution. Apart from speech, the mask also hinders non-verbal communication by facial expressions and lip-reading; the understanding of the other is disturbed, and thus interactions are diminished. Moreover, the mask disturbs facial recognition and identification, which is an additional inconvenience for children at school. The facial expression is concealed, so the presence of a possible smile is invisible and the reading of positive or negative emotions is difficult (25). In addition, the teacher's voice is muffled and distorted, which can affect students' comprehension, especially with the presence of significant background noise in the classroom. We did not ask about hearing impairment, although it was often mentioned in the free answers. All of these phenomena are known to contribute to the disruption of teaching and learning at school, especially for children with pre-existing difficulties.

According to parents, just over one quarter of the children in our study experienced breathing discomfort attributed to the mask. Our questionnaire did not collect whether this discomfort occurred in a child sitting at a desk or during exertion in the playground. These difficulties were frequent (36%) in a student population observed in Poland (21). Studies conducted among adults were most often reassuring; in one study, after 1 h of normal walking with an FFP2 mask, no variations were found in pulmonary tidal volume and respiratory rate (26). Also, wearing a mask did not cause significant variation in PO2 and PCO2 at rest or during sedentary activity (27). During muscular exercise, the results were contradictory: measurements taken during exercise in adults with face masks did not show changes in PO2, muscle oxygenation, or heart rate (28). However, as a precaution, the WHO advises against the use of masks during sports activities (29).

Overall, 27% of parents of children wearing a mask reported visual discomfort caused by fogged glasses. The prevalence of children with glasses in fifth grade is 25%[6]; therefore, fogging impairs the vision of all children who wear glasses. The annoying presence of fogging on glasses was also found in a population of students with a similar prevalence (21). Fogging can be avoided by washing glasses with soapy water (30).

Approximately one-quarter of parents reported in their children cutaneous disorders attributed to mask use. Sweat, saliva, and moisture between the mouth and mask were likely responsible. Erythema of the nose, cheeks, and ears was even more common among nurses wearing surgical masks, but the context was different, including 24 consecutive hours of work (23).

More than two thirds of the children had functional problems related to mask-wearing. We can assume that these disorders were more likely related to the anxious and stressful period of the pandemic than mask-wearing itself. Mood disorders (anxiety, sadness, anguish) were the most frequently mentioned and were present in about half of the children. All factors combined can lead to worry in children: children were afraid of being infected; they constantly heard alarming information broadcast by audio-visual media; they also perceived conversations from their parents worried about the situation and about family members' health, especially grandparents who were at risk. Extra-curricular activities were interrupted and relationships and interactions with peers were diminished. Unrecognized and unheeded by parents, temper tantrums or anger can occur and were seen in almost one-third of children. In a study in Shaanxi Province, China, the most common disorders observed in children during the pandemic were irritability, inattention, agitation, and separation anxiety (31). Sleep disturbances were frequently cited by parents and were twice as frequent as compared with a prevalence of 12–17% in children aged 6–12 years (32). Sleep disorders can in turn lead to increased anxiety, mood disorders, learning difficulties, and eating disorders. Only 11% of parents mentioned eating disorders, anorexia or bulimia. In times of stress, there is an increase in eating food, especially sugary foods, decreased outdoor activity, and increased screen use by children, the association being responsible for excessive weight gain (33).

Our study has several limitations. The first is the questionnaire itself, which consisted of a list of symptoms offered to parents and pediatricians. Even if respondents had the option of adding more symptoms, it was easier to check off those previously offered in the questionnaire. However, the symptoms we proposed were those most often reported in the literature. The second limitation was the absence of information regarding the intensity and severity of the symptoms. However, these symptoms rarely led to additional physician consultations, which suggests that they were not usual. Another limitation was the overrepresentation of women who answered both the parents' and pediatricians' surveys. This finding agrees with the distribution of women in the pediatrician medical occupation. Besides these limitations, our study highlights the importance of thinking about accommodations compatible with a comfortable life for children at school and facilitating their learning in the best conditions. Here we propose some advice for pediatricians, parents, children and teachers to promote and accept wearing a mask (**Table 1**).

[6]Available online at: https://data.education.gouv.fr/explore/dataset/fr-en-sante-enfants-grande-section-et-cm2/export/ (accessed February 11, 2021).

CONCLUSIONS

While waiting for effective and widespread vaccination, wearing a face mask is one of the main barrier measures against COVID-19. To avoid further closure of schools, with deleterious consequences, mask-wearing by children is necessary, even if children do not seem highly contagious. Our study showed a moderate adherence of parents to mask-wearing, which was better in children. The side-effects noted by parents were frequent, even if often benign. Of note, the side-effects were significantly reduced when parents adhered to the mask-wearing measure. Therefore, parents must be motivated by constantly renewing the explanations to their children and the justification for this strategy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

RA, CS, CL, FK, and CD conceived the study, analyzed the data, and wrote the manuscript. SB, CL, and AB performed the statistical analysis. CL, RA, CS, AB, and SB contributed to writing the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.676718/full#supplementary-material

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