

## ORIGINAL RESEARCH

# Prospective assessment of premolar eruption rates following extraction of deciduous predecessors affected by pathological root resorption

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**Abstract**

**Background:** Chronic pulpal infection caused by dental caries often leads to the premature loss of primary molars, which can result in significant root resorption and alveolar bone deterioration, potentially disrupting normal premolar eruption. This study aimed to evaluate the eruption rate of premolar tooth buds following the extraction of pathologic primary molars compared to those following physiologic root resorption. **Methods:** A prospective clinical study included 17 pairs of premolar tooth buds from children aged 6 to 8 years. Each participant had at least one infected primary molar that required extraction (pathological group), with the non-infected antimere serving as the control (physiological group). Pre-extraction bitewing and panoramic radiographs were taken, followed by bitewing radiographs after six months to assess eruption rates. The eruption rate was calculated by measuring the change in the distance of premolar movement toward the occlusal plane between baseline and follow-up radiographs, divided by the number of days between them. Data were analyzed using the Wilcoxon signed-rank test. Information on bone crypt (BC), alveolar bone coverage (ABC), and tooth developmental stage were extracted from panoramic radiographs and identified as variable factors potentially influencing the eruption rate, along with the patient's age, gender, arch type and premolar type. **Results:** Results showed a significantly faster eruption rate in the pathological group (mean:  $0.54 \pm 0.325$  mm/month) compared to the physiological group (mean:  $0.15 \pm 0.163$  mm/month) over an average follow-up period of  $228.2 \pm 43.16$  days ( $p = 0.002$ ). Moreover, a significantly higher absence of BC and ABC was observed in the pathological group compared to controls ( $p = 0.001$ ). **Conclusions:** These findings suggested that premolar eruption was significantly accelerated in children aged 6–8 years who had infected primary molars compared to those without prior infections. **Clinical Trial Registration:** The study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) as TCTR20220530001.

**Keywords**

Root resorption; Premolar; Predecessors; Tooth eruption; Premature loss; Bone crypt; Alveolar bone coverage

## 1. Introduction

The normal process of exfoliation of deciduous molars and the subsequent eruption of premolars is a critical phase in dental development. Exfoliation of deciduous molars begins around 10–12 years of age, driven by the natural resorption of tooth roots or physiologic root resorption, primarily due to the activity of odontoclasts [1]. This physiologic root resorption clears the way for the eruption of permanent premolars, which typically occurs between 10 and 13 years of age [2]. Radiographically, physiologic root resorption is characterized by a reduction in root length, with the most advanced resorption occurring at the apical and interradicular areas, often

demonstrating a close relationship between the resorbing roots of primary teeth and the crowns of the emerging permanent successors [3]. This resorption typically begins on the lingual surface of anterior teeth and in the furcal areas of molars [4].

Pathologic root resorption is an inflammatory process resulting from pulpal infection, typically caused by caries invading the pulpal cavity or the failure of pulp treatment [5]. In pulpal-infected primary teeth, the roots undergo resorption earlier and more aggressively or extensively than the physiologic process, often accompanied by peri-radicular bone resorption and premature loss of the infected teeth [6]. Consequently, the eruption of succedaneous teeth may be delayed or occur prematurely [7]. Teeth that erupt prematurely often ex-

hibit incomplete root formation, with less than half the length achieved compared to the physiological stage of root development [8]. Premolars with shortened roots and anatomical alterations can lead to inadequate retrusive guidance, compromising the proper contact between the palatal cusp of the upper premolars and the distal fossa of the lower premolars. This disruption in occlusal relationships may increase the risk of developing Class II malocclusions, which are characterized by a retruded mandible and a convex facial profile [9]. They may also exhibit incomplete maturation of crown development or morphology, lead to weakened tooth structure [10]. Therefore, it is imperative to inform children and their parents about the necessity for extra care of these premature erupted teeth. Rigorous dental care and prevention programs should be implemented.

The premature loss of primary anterior teeth has been associated with potential space loss, malocclusion, eruption disturbances, speech problems, and impacts on self-esteem [11, 12]. However, some studies suggest these consequences may not be significant [13, 14]. More comprehensive research is needed to fully understand the effects and guide clinical interventions [15]. In contrast, the premature loss of primary molars is widely recognized as particularly critical, often resulting in chewing difficulties, space loss and other orthodontic complications [16, 17]. The edentulous space resulting from premature loss of primary molars is typically preserved for the erupting premolar through the utilization of a space maintainer. When determining the suitability for inserting the space maintainer, one must consider the amount of alveolar bone coverage (ABC). It is noteworthy that tooth emergence through ABC, with a thickness of 1 mm, requires approximately 4 to 6 months [18–20]. In instances of early loss of primary molars with pathologic root resorption, the rate of premolar eruption may vary due to extensive bone resorption within the bony crypt or the peri-radicular area [7]. This situation raises concerns about both the treatment planning of the space maintainer for the patient and the additional care required for prematurely erupted premolars.

Previous studies have shown that premolar eruption is generally delayed in children who lose deciduous molars prematurely at ages four and five. However, this delay gradually shifts to accelerated eruption by ages eight to ten [10, 21]. Additionally, apical periodontitis in primary teeth can delay or alter the development and eruption path of permanent successors [7, 10, 22]. However, in some cases, root resorption of primary teeth has been found to have no significant effect on the development of permanent successors [6]. Based on these findings, the current study hypothesizes that premolar eruption rates will differ depending on whether the extraction of predecessor teeth was due to pathological or physiological root resorption. Therefore, this study aimed to compare the eruption rates of premolars after the extraction of predecessors affected by pathological root resorption with those following predecessors affected by physiological root resorption.

## 2. Materials and methods

### 2.1 Sample size calculation

The sample size for this study was determined using G\*power software (Version 3.1.9.7, Franz Faul, Universität Kiel, Kiel, SH, Germany), employing a two-dependent means (matched pairs) *t*-test with a Type I error of 0.05 and a beta error of 0.2. A large effect size ( $d = 0.8$ ) was applied based on prior research demonstrating a significant impact on the variables of pathologic root resorption and apical periodontitis [7, 22]. The minimum required sample size was calculated to be 15 pairs of teeth.

### 2.2 Participants

Children who received dental treatment at Naresuan University Dental Hospital, Thailand between September 2022 and September 2023 and met the inclusion criteria were enrolled in the study. The inclusion criteria were children aged 5–9 years who had at least one primary molar, either upper or lower, first or second, with periapical pathology indicated for extraction (pathological group), while the corresponding antimeres remained intact with normal radiographic findings (physiological group). This age range was selected to capture participants at a critical stage of premolar eruption, ensuring their suitability for the study. Around age 5, the first premolar root begins to develop, marking the onset of tooth eruption. By age 9, children generally experienced the natural exfoliation of primary molars, which reduces likelihood of identifying suitable candidates. Furthermore, exclusion criteria included children with any underlying diseases, syndromes, or conditions that affected craniofacial development or bone metabolism, as well as individuals with orthodontic problems. The antimeres with previous pulp treatment or inadequate radiographs (*e.g.*, distortion, overlapping or poor contrast) were also excluded.

### 2.3 Data collection

Radiographs (bitewing and panoramic) for transitional dentition patients, following American Academy of Pediatric Dentistry (AAPD) guidelines were acquired by both a researcher and a pediatric dentist [23]. All bitewing radiographs were obtained using a standardized intraoral X-ray unit (Veraview iX V080, J. Morita, Kyoto, Japan) equipped with size 2 photostimulable phosphor plates (Image Plates Plus, DÜRR DENTAL, BW, Germany) and a bite-wing stabilization device. To ensure consistent patient positioning for the intraoral radiograph, the Alar-Tragus line was aligned parallel to the floor [24]. Furthermore, the patient's midsagittal plane was positioned perpendicular to the Alar-Tragus line [25]. The vertical angulation of the X-ray beam was set between 0 to +10 degrees relative to the alar-tragus line plane, while the horizontal angulation was adjusted to ensure a perpendicular alignment with the image receptor [26]. The panoramic examination was performed using the Veraview X800 (J. Morita, Kyoto, Japan). The exposure factors were set according to the manufacturer's recommendations.

Following the baseline radiographic examination, patients underwent the extraction of the primary molars exhibiting pathological root resorption within one month. During the extraction procedure, careful attention was given to avoid

applying excessive force to the primary molar, particularly in the subgingival area, to prevent any interference with the underlying premolar tooth bud. All necessary dental treatments were carried out according to each participant's comprehensive treatment plan, including the placement of space maintainers when indicated [27, 28]. The indication for space maintainers was based on the presence of ABC of more than 1 mm over the premolar tooth bud, as assessed from the baseline bitewing radiographs [27, 28]. Additionally, participants were required to demonstrate adequate oral hygiene and the ability to attend follow-up appointments. The space maintainers used were of the fixed type, including band and loop, lingual holding arch and Nance appliances. During the recall period, posterior bitewing radiographs were obtained at intervals ranging from 6 to 12 months following the baseline radiographic examination [23].

Panoramic radiographs were used to collect data from the baseline radiograph on the presence of bone crypt (BC) and ABC over the premolar tooth bud, as well as on the arch type (maxillary or mandibular), the type of premolar (first or second), and the stage of premolar root development as classified by Demirjian [29, 30]. However, since panoramic radiographs were only taken during the baseline phase, the root development level of the premolar tooth, BC and ABC were not assessed at that time. Both baseline and follow-up bitewing radiographs were employed to assess the rate of premolar eruption. In addition, demographic information, including gender and age, was extracted from the patient's charts.

## 2.4 Calibration and radiographic interpretation

The calibration process involved locating reference points, measuring and interpreting both the bitewing and panoramic radiographs, from which the BC, ABC and Demirjian's classifications were determined. The radiographic parameters used for calibration included the identification of all reference points on both bitewing and panoramic radiographs, as well as the measurement methods for all distances.

For inter-examiner calibration, one researcher interpreted the radiographs, and the interpreter's assessments were compared with those of a pediatric dental specialist and an oral radiologist, using 20 radiographs for each comparison. Intra-examiner calibration comprised two rounds of interpretation from the same set of 20 bitewing radiographs and 20 panoramic radiographs, with an interval of more than one week between the rounds. The kappa value ranged from 0.81–0.90 for the inter-examiner calibration and 0.93–0.94 for the intra-examiner calibration, both exceeding 0.80 suggesting an almost perfect agreement [31].

Radiographic interpretations were conducted by a researcher and a pediatric dentist using Uniweb Software Version 8.1.1833.0 (Carestream Health, Inc., Rochester, NY, USA) on the same monitor and computer throughout the study.

### 2.4.1 Rate of tooth eruption

The rate of tooth eruption was determined by measuring the changes in distance between reference points on sequential

bitewing radiographs [21, 32–34]. Bitewing radiographs were utilized for this purpose, as their parallel angulation provided more accurate proportions and a better evaluation of bone levels compared to panoramic radiographs [35–37]. In addition, it reduced patient radiation dose compared to panoramic radiographs [38]. All reference points were located on fixed anatomical landmarks, including bony structures or non-erupting teeth with complete root formation, to avoid any movement or positional changes of those points [35].

To standardize measurements across baseline and follow-up bitewing radiographs (Fig. 1A,B), the study defined a reference line (ab line) extending from point "a" the cemento-enamel junction (CEJ) of the primary tooth mesial to the affected primary molar or antimere, to point "b" the CEJ of the primary tooth distal to the affected primary molar or antimere. This reference line was then employed to calculate the tooth eruption rate (mm/month) using the formula  $(y1 - y3)/D \times 30$ , where "D" represented the number of days between the baseline and follow-up radiographs (follow-up period). Several other key measurements were also obtained from the radiographs:

"d": Defined as the cusp tip of the reference tooth located closest to the affected primary molar, identified as the same point in both the baseline and follow-up radiographs (Fig. 1A,B).

"h1" and "h2": Represented the perpendicular distance between "d" and the ab line on the baseline and follow-up radiographs, respectively (Fig. 1A,B).

"c": Defined as the cusp tip of the premolar located beneath the affected primary molar, identified as the same point in the baseline and follow-up radiographs (Fig. 1A,B).

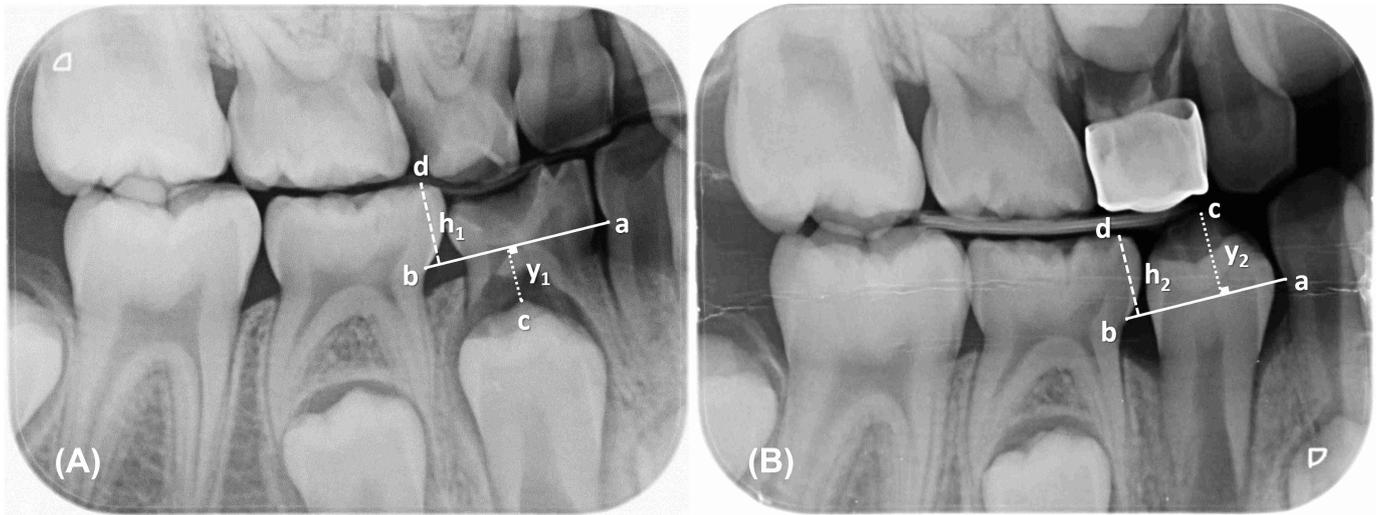
"y1": This variable denoted the perpendicular distance between the cusp tips of the premolars and the ab line on the baseline radiograph (Fig. 1A).

"y2": This variable represented the same perpendicular distance measured on the follow-up radiograph (Fig. 1B).

To mitigate linear distortion in one of the three axes in 2D imaging, the h1/h2 ratio was used to calculate an adjusted distance (y3). This adjustment compensated for magnification discrepancies between the baseline and follow-up radiographs, thereby addressing measurement inaccuracies caused by radiographic distortion.

### 2.4.2 BC and ABC

BC was determined by examining the white continuous outline over the tooth bud's crown, extending from the most mesial to the most distal aspect (MD) as observed on the panoramic radiograph. BC was classified as "present" if it covered half or more of the mesial-distal (MD) width (extending beyond the black dashed line), and as "absence" if it covered less than half of the MD width (Fig. 2A–C). For assessing ABC, the evaluation focused on the presence of trabecular bone over the premolar tooth crown. "Presence" was defined as coverage equal to or greater than half of the trabecular bone volume between the furcation and the occlusal plane of the tooth bud. Conversely, "absence" indicated less than half of the trabecular bone volume covering the tooth bud (Fig. 2A–C).



**FIGURE 1. Illustrates the measurement of the y distance.** (A) Baseline radiograph showing: a: The CEJ of the primary tooth mesial to the pathologic primary molar or antimere. b: The CEJ of the primary tooth distal to the pathologic primary molar or antimere. c: The cusp tip of the succedaneous premolar. d: The cusp tips of the reference tooth. h: The height of the crown of the reference tooth. y: The perpendicular distance between the c and the ab line. (B) Follow-up radiograph indicating the same reference points.



**FIGURE 2. Evaluation of BC and ABC over the premolar tooth bud from panoramic radiographs.** The horizontal black arrow line indicates the distance from the most mesial to the most distal aspect (MD) of the premolar tooth bud. The small black arrows highlight the BC, the vertical dashed black line represents half the distance of the MD, and the vertical white arrow indicates the area of the ABC. (A) The tooth bud with the presence of both BC and ABC. (B) The tooth bud with the absence of BC and ABC. (C) The tooth bud with the presence of BC but the absence of ABC. ABC: alveolar bone coverage.

## 2.5 Statistic analysis

Data were processed and analyzed using the Statistical Package of the Social Sciences (Version 26, IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated, including mean, standard deviation, frequency and percentage. The presence or absence of BC and ABC in the pathological and physiological groups were compared using Chi-square tests. Statistical significance was set at  $p < 0.05$ . A comparison of premolar eruption rates between the pathological and physiological groups was conducted by calculating the mean eruption rate, utilizing the Wilcoxon signed-rank test due to the non-significance of the normality test ( $p < 0.05$ ).

## 3. Results

## 3.1 Descriptive data

An initial screening identified 24 tooth pairs from 20 children who met the inclusion criteria at baseline. During the follow-up period exceeding 6 months, seven pairs were excluded for the following reasons: unqualified bitewing radiographs ( $n = 2$ ), loss to follow-up ( $n = 3$ ), and failure to extract the tooth within 1 month of the panoramic radiograph ( $n = 2$ ). Consequently, the final analysis included 17 tooth pairs (14 children) divided into pathological and physiological groups, with an average follow-up period of 228.2 days (standard deviation (SD) = 43.16). Table 1 presents the distribution and frequency of samples categorized by gender, age group, arch type, premolar type and Demirjian's classification. Table 2 summarizes the comparison of BC and ABC availability between the pathological and physiological groups. Interestingly, premolars in the pathological group exhibited a significantly higher absence of both BC and ABC compared to

the physiological group ( $p = 0.001$ ).

**TABLE 1. Descriptive data of patients and their premolars in the study.**

Variables	Number of teeth (%)	
	Pathological group	Physiological group
Gender		
Male	9 (52.9)	9 (52.9)
Female	8 (47.1)	8 (47.1)
Age		
6 yr	3 (17.6)	3 (17.6)
7 yr	4 (23.5)	4 (23.5)
8 yr	10 (58.8)	10 (58.8)
Arch type		
Upper	7 (41.2)	7 (41.2)
Lower	10 (58.8)	10 (58.8)
Type of premolar		
First	9 (52.9)	9 (52.9)
Second	8 (47.1)	8 (47.1)
Demirjian's classification		
D	7 (41.2)	7 (41.2)
E	8 (47.0)	8 (47.0)
F	2 (11.8)	2 (11.8)
Total	17 (100.0)	17 (100.0)

**TABLE 2. Presence of BC and ABC in pathological and physiological groups.**

Variables	Number of teeth (%)		<i>p</i> -value
	Pathological group	Physiological group	
BC			
Presence	5 (29.4)	15 (88.2)	0.001*
Absence	12 (70.6)	2 (11.8)	
ABC			
Presence	5 (29.4)	15 (88.2)	0.001*
Absence	12 (70.6)	2 (11.8)	
Total	17 (100.0)	17 (100.0)	

*Statistical analysis was performed using Chi-square test (\* $p < 0.05$ ). BC: bone crypt; ABC: alveolar bone coverage.*

### 3.2 Rate of premolar eruption

Table 3 presents the mean eruption rates of premolars in the pathological and physiological groups. Premolars in the pathological group exhibited a significantly faster average rate compared to those in the physiological group ( $p = 0.002$ ).

## 4. Discussion

This study aimed to investigate the eruption rate of premolars in cases where the predecessor tooth exhibited either patho-

**TABLE 3. Eruption rate of premolars in the pathological and physiological groups.**

Eruption rate (mm/mo)	Pathological group (N = 17)	Physiological group (N = 17)	<i>p</i> -value
Mean (SD)	0.54 (0.325)	0.15 (0.163)	0.002*
Minimum–Maximum	0.03–1.07	0.00–0.51	

*Statistical analysis was performed using the Wilcoxon signed-rank test (\* $p < 0.05$ ). SD: standard deviation; mo: month.*

logic root resorption or physiologic root resorption. After an average follow-up period of  $228.2 \pm 43.16$  days, the eruption rate of premolars in the pathological group was significantly faster compared to those in the physiological group ( $p = 0.002$ ). Additionally, premolars in the pathological group exhibited a significantly greater absence of both BC and ABC compared to those in the physiological group ( $p = 0.001$ ).

The premature eruption of premolars on the side with premature loss of primary molars, compared to the opposite side without pathology, has been reported previously; however, without calculating or comparing of the eruption rate [21, 39]. Delayed eruption of premolars was found in the very young age group (4–5 years old); thereafter, the rate slightly increased and accelerated if the early loss of the primary molar predecessor occurred at an age older than eight years [21]. The current study observed a significantly faster average eruption rate for premolars in the pathological group compared to the physiological group among children aged 6 to 8 years. This finding aligns with the observed significantly greater absence of BC and ABC surrounding the premolar tooth buds in the pathological group compared to the physiological group. Another variable that could have been considered is the diagnosis of the periapical tissues of the deciduous tooth. A necrotic tooth with an abscess or chronic periapical periodontitis with a drainage fistula might have influenced the degree of alveolar bone destruction [40]. Therefore, the lack of BC and ABC suggested a potential for extraosseous eruption, a process characterized by faster tooth movement compared to the intraosseous eruption typically observed in the physiological group [41]. These findings supported existing literature, as Fanning *et al.* [33] demonstrated that destruction of the surrounding bone of primary molars could lead to increased premolar eruption. The concept of tooth eruption is closely linked to bone resorption and deposition. One theory proposed that the absence of bone resistance facilitates unimpeded eruption [42]. Our study design included a pathological group defined by carious primary molars requiring extraction, suggesting a potential for chronic and severe infection. This chronic infection, often caused by bacteria from a diseased pulp, could have spread through the anatomy of primary molars, which contain multiple accessory canals and a porous floor in the pulp chamber. The infection likely spread to the surrounding alveolar bone, which may explain the observed accelerated eruption in the pathological group [22].

In this study, we found that premolars from pathological and

physiological groups were distributed across all age groups, genders, arch types, premolar types, and Demirjian's classifications. Additional research has shown that premolar development can be influenced by the type and level of root resorption. Wahono *et al.* [22] identified a significant correlation between pathologic root resorption and premolar development in stages D and E among girls aged 6 to 8 years. Conversely, Mulia *et al.* [6] found no such correlation among boys aged 7 to 8 years old. Both studies utilized measurements of root resorption levels to examine this relationship with tooth growth stages. Recent research conducted by Li *et al.* [7] demonstrated that periapical disease of primary molar predecessors either slowed down or accelerated the developmental stage or affected the shape or direction of successors in children aged 4 to 10 years. Furthermore, Patil *et al.* [10] observed that greater pathologic root resorption of predecessors was associated with more follicular damage of premolar successors in children of the same age group. This study did not find any correlation between arch type and type of premolar with the rate of premolar eruption in the pathological group. Conversely, Kerr *et al.* [43] found that premolar eruption was accelerated in the upper arch following the premature loss of primary molars, but slightly slower in the lower arch. These collective findings highlight the intricate interactions between root resorption, periapical disease, dental follicular health and alveolar bone status in influencing premolar eruption patterns, underscoring the need for comprehensive understanding and management of these factors in clinical practice.

In this study, the antimere premolar beneath the intact primary molar was used as a control to manage confounding factors arising from inter-individual differences and environmental variables that could influence premolar eruption rates. This approach controlled for variables such as the maxilla-mandibular skeletal pattern, while accounting for uncontrolled factors including dietary habits, genetic traits and indigenous microflora. It reinforced the rationale for the split-mouth design, allowing each patient to serve as their own control, which facilitated more accurate comparisons and minimized the impact of external variables on the study's outcomes. Additionally, this prospective approach provided more accurate and comprehensive results compared to cross-sectional studies or retrospective data collection from patient records. However, there were several limitations. Firstly, patients who required the extraction of primary molars often had multiple severely decayed teeth, including the antimere, which led to a limited number of participants in the sample groups. Secondly, to capture both the primary molars and premolar tooth buds simultaneously, size 2 periapical radiographs were necessary. However, obtaining high-quality radiographs without distortion in young children or those with a small oral cavity using size 2 radiographs proved to be quite challenging. Thirdly, follow-up radiographs were taken at variable intervals ranging from 6 to 12 months. This variability made it challenging to establish consistent comparisons over time, as premolar eruption may not occur at a constant rate but rather exhibit fluctuating eruptive activity. Furthermore, the small sample size limited the ability to perform statistical analyses on the influence of potential factors on the eruption rate between the two groups. Lastly, a common issue in prospective studies,

participant loss due to non-return for follow-up examinations, was also present.

Future research could explore the use of extraoral bitewing radiographs as an alternative imaging technique for assessing premolar buds, adjacent areas, and detecting proximal caries, especially for high-risk children. These radiographs could be obtained using the same panoramic radiography machine, allowing for the simultaneous acquisition of two bitewing images (right and left). Laboratory research has demonstrated the effectiveness of extraoral bitewing radiographs in diagnosing proximal caries of primary teeth, showing similar accuracy to microscopic examination when compared to intraoral bitewing radiographs [44]. Furthermore, conducting longitudinal follow-up studies on patients until the emergence of premolar teeth could provide a more accurate determination of premolar eruption rates. Additionally, expanding the sample size and age range, along with collecting data on other consequential factors following the extraction of pathologic primary molars (such as tooth shape, eruption direction, and maturation of successors), would have enhanced the precision of research findings and contributed to a better understanding of the factors influencing the rate and manner of premolar successor eruption.

## 5. Conclusions

This study investigated the eruption dynamics of premolars following the extraction of primary molars with pathological root resorption compared to those on the physiologically developing antimere side in six- to eight-year-old children. The results demonstrated a significantly faster average eruption rate of premolars in the pathological group compared to the physiological group. Furthermore, premolars in the pathological group exhibited a significantly greater absence of BC and ABC surrounding the tooth bud.

## ABBREVIATIONS

BC, bone crypt; ABC, alveolar bone coverage.

## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## AUTHOR CONTRIBUTIONS

RS—conceived and designed the study, collected and analyzed the data, and led the manuscript writing. RP—collaborated in designing the study, collected and analyzed data, and contributed to the writing. PN—was responsible for data curation and statistical analysis. RK, ST and WS—collaborated in designing the study, and contributed to the writing and editing. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Naresuan University Institutional Review Board (IRB P1-0099/2565). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s), and assent was obtained from the children, for the use of their information in this study.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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