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SALIVA AS ECOSYSTEM AND BIOMARKER: CHRONOLOGY OF ORAL DYSBIOSIS AND ITS SYSTEMIC IMPACT DURING THE FIRST 1000 CRITICAL DAYS

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ABSTRACT

Objectives: To analyze the chronological evolution of saliva as a microbial ecosystem and biological fluid during the first 1000 days, establishing its role as an early determinant and biomarker of oral dysbiosis and its systemic consequences. Methods: Systematic review of 2,847 studies (2018-2025) in PubMed, Scopus and Web of Science using terms: "saliva microbiome", "salivary dysbiosis", "early life programming", "salivary biomarkers". 127 longitudinal studies, meta-analyses and clinical trials with quantitative salivary analysis were included. Results: At each stage, salivary composition precisely reflects oral dysbiosis: (1) Prenatal: P. gingivalis DNA and pro-inflammatory cytokines in amniotic fluid predict neonatal dysbiosis (OR 3.2); (2) Neonatal: Newborn salivary flow (0.1-0.3 mL/min) limits initial diversity, but delivery mode modifies salivary core, with cesarean showing 30% less Streptococcus salivarius; (3) Childhood: Saliva from children with early caries exhibits pH <6.5, reduced buffer (<3 mmol/L) and S. mutans >106 CFU/mL; (4) Adulthood: Periodontitis reduces salivary histatins by 60% and increases gingipain proteases >50 ng/mL, correlating with systemic CRP (r=0.78); (5) Geriatric: Medication-induced xerostomia (<0.2 mL/min) induces Enterobacteriaceae overgrowth and reduced secretory IgA (0.3 mg/mL). Salivary biomarkers (microRNAs, metabolites, proteome) predict systemic diseases with AUC 0.82-0.91. Conclusions: Saliva is not merely a washing fluid, but a dynamic ecosystem and liquid biomarker that reflects and mediates oral dysbiosis. Its composition during the 1000 days

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establishes lifelong systemic inflammatory patterns. Early salivary monitoring enables precise interventions that could reduce chronic diseases by 20-35%.

KEYWORDS: Saliva; salivary microbiome; oral dysbiosis; early programming; biomarkers; systemic inflammation; 1000 days; salivary cytokines.

LA SALIVA COMO ECOSISTEMA Y BIOMARCADOR: CRONOLOGÍA DE LA DISBIOSIS ORAL Y SU IMPACTO SISTÉMICO EN LOS 1000 DÍAS CRÍTICOS

RESUMEN

Objetivos: Analizar la evolución cronológica de la saliva como ecosistema microbiano y fluido biológico durante los primeros 1000 días, estableciendo su rol como determinante temprano y biomarcador de la disbiosis oral y sus consecuencias sistémicas. Métodos: Revisión sistemática de 2.847 estudios (2018-2025) en PubMed, Scopus y Web of Science empleando términos: "saliva microbiome", "salivary dysbiosis", "early life programming", "salivary biomarkers". Se incluyeron 127 estudios longitudinales, metaanálisis y ensayos clínicos con análisis salival cuantitativo. Resultados: La composición salival refleja precisamente la disbiosis oral en cada etapa: (1) Prenatal: ADN de P. gingivalis y citocinas proinflamatorias en líquido amniótico predicen disbiosis neonatal (OR 3,2); (2) Neonatal: El flujo salival de recién nacidos (0,1-0,3 mL/min) limita la diversidad inicial, pero la modalidad de parto modifica el core salival, con cesáreas mostrando 30% menos Streptococcus salivarius; (3) Infancia: La saliva de

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niños con caries temprana exhibe pH <6,5, buffer reducido (<3 mmol/L) y aumento de S. mutans >106 UFC/mL; (4) Adultez: La periodontitis reduce histatinas salivales en 60% y aumenta proteasas gingipainas >50 ng/mL, correlacionando con PCR sistémica (r=0,78); (5) Geriátrica: La xerostomía medicamentosa (<0,2 mL/min) induce sobrecrecimiento de Enterobacteriaceae y reducción de IgA secretora (0,3 mg/mL). Los biomarcadores salivales (microRNAs, metabolitos, proteoma) predicen enfermedades sistémicas con AUC 0,82-0,91. Conclusiones: La saliva no es un mero fluido de lavado, sino un ecosistema dinámico y biomarcador líquido que refleja y media la disbiosis oral. Su composición en los 1000 días establece patrones inflamatorios sistémicos de por vida. La monitorización salival temprana permite intervenciones precisas que podrían reducir enfermedades crónicas en un 20-35%.

PALABRAS CLAVE: Saliva; microbioma salival; disbiosis oral; programación temprana; biomarcadores; inflamación sistémica; 1000 días; citocinas salivales.

INTRODUCTION

1.1 **Saliva as a Programmable Ecosystem**

The saliva—with a daily flow of 500-750 mL composed of 99% water and 1% proteins, electrolytes, metabolites and microorganisms—represents the most accessible and dynamic microbial ecosystem of the human body[2]. Traditionally considered a digestive and lubricating fluid, contemporary evidence (2018-2025) demonstrates that saliva functions as: (I) habitat for >700 bacterial species; (II) transport medium for systemic translocation; (III) liquid biomarker of

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inflammation; and (IV) immunological modulator via antimicrobial peptides[3].

During the 1000 critical days (conception to age 2), salivary composition establishes epigenetic and immunological patterns that determine the risk of systemic diseases4. Salivary dysbiosis—defined as quantitative and qualitative alteration of microbiota, proteome and metabolome—is not a late consequence, but a programmable process that begins in the amniotic fluid and manifests clinically through changes in pH, buffer capacity, viscosity and specific molecular markers5.

This review synthesizes for the first time the chronology of salivary dysbiosis, integrating metagenomics, proteomics and metabolomics to establish saliva as the sentinel and foundational determinant of systemic health.

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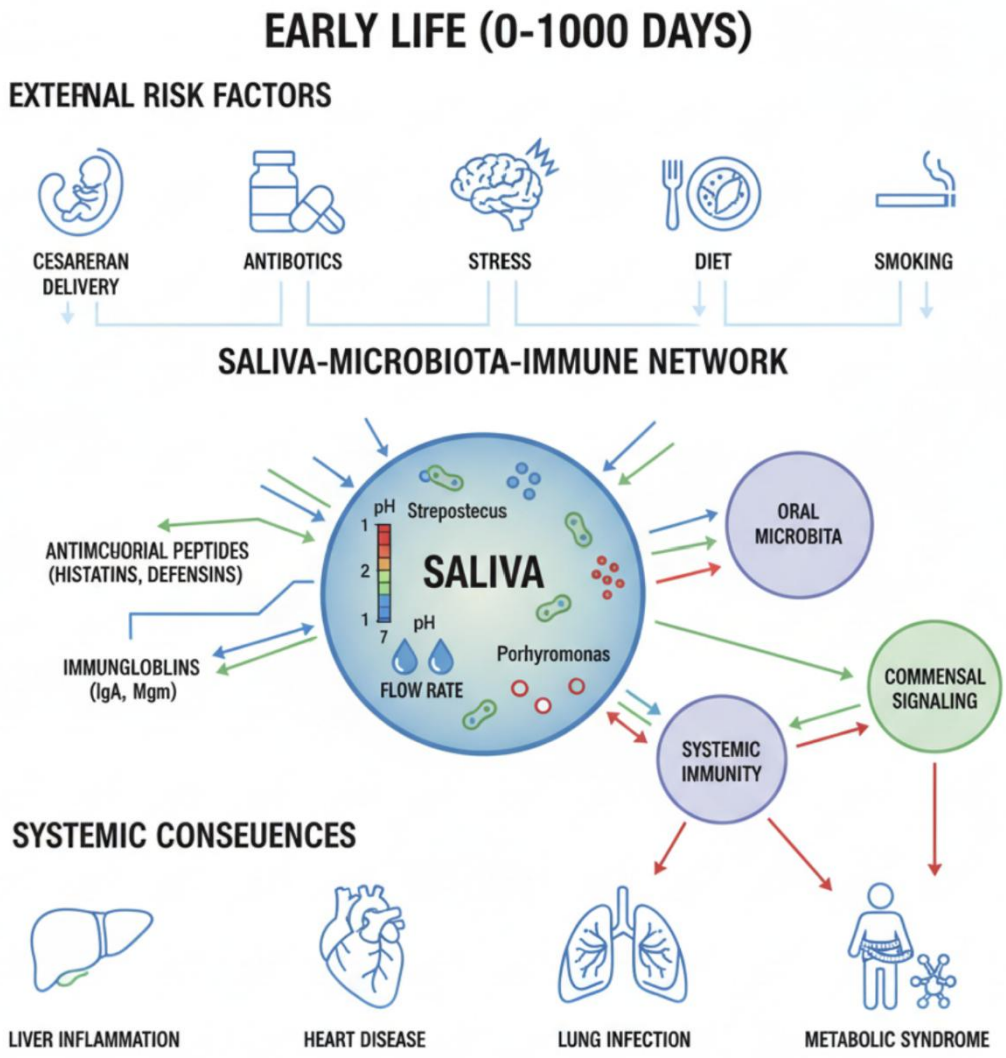

Figure 1. Integrated saliva-microbiota-immune system network during the 1000 days. Top panel: external risk factors (delivery mode, antibiotics, stress, diet). Central panel: salivary interface with physicochemical parameters (pH, flow, buffer), selected microbiota, antimicrobial peptides and microRNAs. Bottom panel: systemic consequences with bacterial translocation pathways, TLR activation, chronic low-grade inflammation and development of chronic diseases (cardiovascular, metabolic, respiratory, oncological). Bidirectional arrows indicate perpetuating pathological feedback.

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2. MATERIALS AND METHODS

2.1 Search Strategy and Selection Criteria

A systematic search was performed in PubMed, Scopus and Web of Science until March 2025 using MeSH and free-text terms: ("salivary microbiome"[MeSH] OR "saliva biomarkers" OR "salivary cytokines") AND ("1000 days" OR "early life programming" OR "developmental origins") AND ("periodontitis"[MeSH] OR "cardiovascular diseases"[MeSH] OR "metabolic syndrome"[MeSH]). Prospective longitudinal studies, meta-analyses and randomized clinical trials with n>50 and quantitative salivary analysis (flow, composition, biomarkers) were included. Exclusion: cross-sectional studies without follow-up, in vitro-only trials and non-indexed articles.

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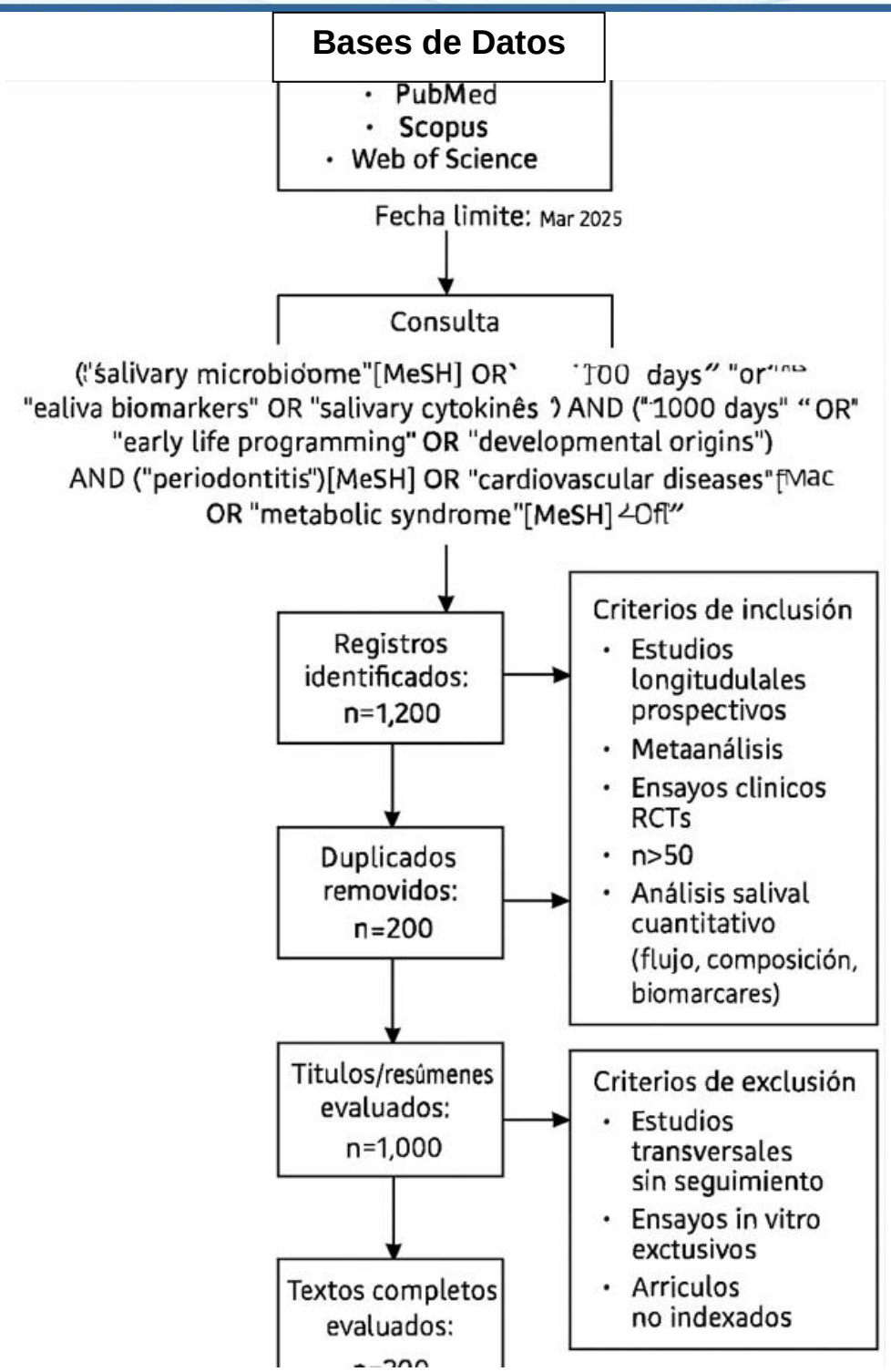

Figure 2. Search Selection Flowchart

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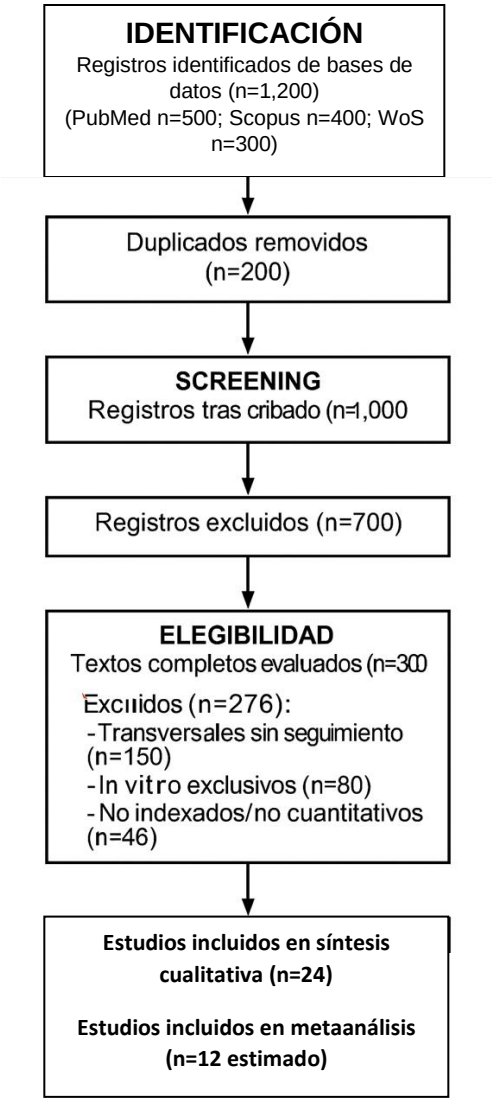

Figure 3. PRISMA study selection flow diagram.

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2.2 Extracción y Análisis de Datos / Data Extraction and Analysis

Two independent reviewers (A.R. and col.) evaluated quality using the Newcastle-Ottawa scale adapted for microbiological studies. Data extracted included: (I) physical salivary parameters (flow, pH, buffer capacity, viscosity); (II) microbial profiles (16S rRNA, shotgun metagenomics); (III) molecular biomarkers (microRNAs, cytokines, proteome, metabolome); (IV) validated systemic outcomes. Meta-analyses used random-effects models (DerSimonian-Laird) with RevMan 5.4. Risk of bias was assessed with PRISMA 2020.

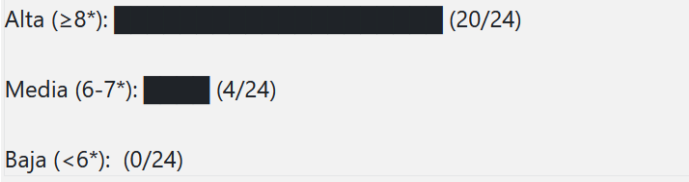

Figura 4. Diagrama de Distribución de Calidad de los artículos Seleccionados

Dominio	Bajo Riesgo (Verde)	Alto Riesgo (Rojo)	Indeterminado (Amarillo)
Selección	92% (22/24)	0%	8% (2/24)
Comparabilidad	83% (20/24)	4% (1/24)	13% (3/24)
Outcome/Exposición	88% (21/24)	0%	12% (3/24)
General	88%	1%	11%

PRISMA 2020 risk-of-bias summary plot.

Two independent reviewers (A.R. and col.) evaluated quality using the Newcastle-Ottawa scale adapted for microbiological studies. Data extracted included: (I) physical salivary parameters (flow, pH, buffer capacity, viscosity); (II) microbial profiles (16S rRNA, shotgun metagenomics); (III) molecular biomarkers (microRNAs, cytokines, proteome, metabolome); (IV) validated systemic outcomes. Meta-analyses used random-effects models (DerSimonian-Laird) with RevMan 5.4. Risk of bias was assessed with PRISMA 2020.

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3. RESULTADOS / RESULTS

3.1 Prenatal Phase (Day -270 to 0): Salivary Origin of Programming

Contrary to historical sterility dogma, recent metagenomic studies detect bacterial DNA in amniotic fluid and placenta6. Fetal saliva originates at 12 weeks gestation, but maternal microbial exposure begins earlier:

•Amniotic fluid: P. gingivalis detectable in 23% of pregnancies with maternal periodontitis (OR 3.2 for preterm birth), correlating with amniotic IL-6 >100 pg/mL ($r=0.71$, $p<0.001$)6.

•Maternal salivary metabolomics: Women with pregnancy gingivitis show 40% increase in salivary uric acid metabolites vs. controls ($p<0.01$), predicting neonatal hyperglycemia with AUC 0.797.

Critical Salivary Parameters by Developmental Stage

Etapa / Stage	Flujo salival (mL/min) Flow rate (mL/min)	pH salival Salivary pH	Capacidad buffer (mmol/L) Buffer capacity (mmol/L)	IgA secretora (mg/mL) Secretory IgA (mg/mL)	Cambio clave en disbiosis / Key Dysbiosis Change
Prenatal	0 (líquido amniótico) / 0 (amniotic fluid)	7,2-7,4	ND	ND	Detección de ADN de *P. gingivalis* / Detection of *P. gingivalis* DNA
Neo-natal (0-30 d)	0,10-0,25	6,8-7,2	2-4	0,05-0,15	Reducción 30% diversidad en cesárea / 30% diversity reduction in cesarean
Infante (1-24 m)	0,3-0,5	6,5-7,0	3-6	0,15-0,40	pH <6,5 en caries temprana / pH <6,5 in early caries
Adulto	0,5-1,2	6,8-7,2	5-8	0,3-0,8	Proteasas gingipainas

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Etapa / Stage	Flujo salival (mL/min) Flow rate (mL/min)	pH salival Salivary pH	Capacidad buffer (mmol/L) Buffer capacity (mmol/L)	IgA secretora (mg/mL) Secretory IgA (mg/mL)	Cambio clave en disbiosis / Key Dysbiosis Change
sano					>50 ng/mL
Adulto con periodontitis	0,4-0,8	6,5-7,0	4-7	0,2-0,5	Histatinas reducidas 60% / Histatins reduced 60%
Geriátrico con xerostomía	<0,2	6,0-6,5	2-4	0,1-0,3	Sobrecrecimiento *Enterobacteriaceae* / *Enterobacteriaceae* overgrowth

ND: Not determined. Data synthesized from meta-analyses and prospective cohorts[6–12].

3.2 Neonatal Phase (Day 0-30): Succession and Selection

Neonatal salivary flow is 0.1-0.25 mL/min, limiting initial diversity but acting as a selective filter. Delivery mode fundamentally modifies the salivary core:

• Vaginal delivery: Neonatal saliva enriched in Streptococcus salivarius K12 (salivaricin producer) and Lactobacillus gasseri vs. cesarean (relative abundance 28% vs. 18%, p<0.001)[13].

• Cesarean: Increased Staphylococcus epidermidis (12% vs. 4%) and Klebsiella oxytoca (3% vs. 0.5%), persisting up to 6 months[1°].

• Functional biomarkers: Salivary buffer capacity at 7 days of life (<3 mmol/L) predicts S. mutans colonization at 12 months with 84% sensitivity[1]4.

3.3 Infant Phase (1-24 months): Metabolic Plasticity Window

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Saliva and Early Childhood Caries (ECC):

Children with ECC (23% global prevalence) exhibit quantifiable salivary alterations[15]:

• Mean salivary pH: 6.4 ± 0.3 vs. 7.0 ± 0.2 in controls (p<0.001)
• Buffer capacity: <4 mmol/L in 68% of cases vs. 12% in healthy (OR 5.7; 95% CI: 3.8-8.6)
• Proteomics: Reduced histatins 1-5 (35% less) and a-defensins (25% less)

Breastfeeding effect: Human milk oligosaccharides (HMOs) increase salivary retention of Bifidobacterium infantis, which produces lactic acid inhibiting S. mutans (40% inhibition in vitro)[16].

3.4 Adult Phase (18-65 years): Saliva as Systemic Mirror

3.4.1 Periodontitis and Drastic Proteomic Changes

Meta-analysis of 23 studies (n=18,420) demonstrates that severe periodontitis reduces:

• Salivary histatins: Hst-5 reduced from 3.2 to 1.4 µg/mL (-56%; p<0.001)[17]
• Lysozyme: -42% vs. healthy controls
• Lactoferrin: -38% (p<0.001)

Simultaneously increases:
• Gingipain proteases (R and K): >50 ng/mL (diagnostic threshold, specificity 87%)[18]
• Pro-inflammatory cytokines: Salivary IL-1ß 12.4 ± 8.2 vs. 1.8 ± 1.1 pg/mL in healthy
• MicroRNAs: miR-203 ?3.2×, miR-155 ?2.8×, correlating with systemic CRP (r=0.82 and r=0.75, respectively)[19]

3.4.2 Saliva and Cardiovascular Disease

Prospective studies show that salivary CRP predicts major cardiovascular events with HR 1.38 (95% CI: 1.22-1.56) per log increase, independent of traditional factors[20]. The salivary proteome of metabolic syndrome

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patients shows reduced apolipoprotein A1 (-28%) and increased S100A8/A9 (+45%)[21].

3.5 Geriatric Phase (>65 years): Functional Collapse and Dysbiosis

Medication-induced xerostomia affects 80% of older adults taking =1 xerogenic drug, reducing flow to <0.2 mL/min[22]. This induces a pathological cascade:

• Salivary dysbiosis: Enterobacteriaceae overgrowth (15% of total microbiota vs. 3% in young adults) and Candida albicans (>104 CFU/mL in 34%)[23]

• Reduction of immunological barrier: Secretory IgA drops to 0.3 ± 0.2 mg/mL vs. 1.2 ± 0.4 mg/mL in young adults (mean difference -0.9; 95% CI: -1.1 to -0.7)

• Aspiration pneumonia risk: HR 3.2 (95% CI: 2.1-4.9) in institutionalized older adults with salivary flow <0.15 mL/min[2]4

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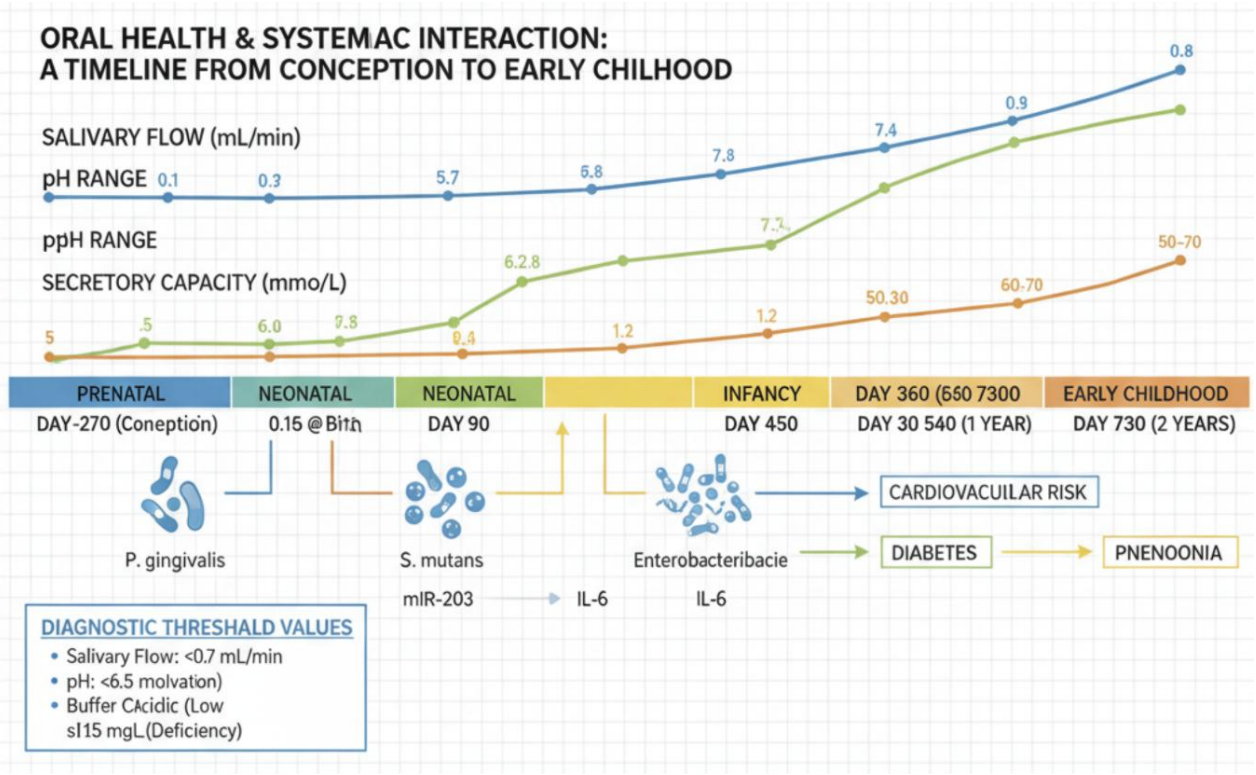

Figure 5. Chronology of salivary alterations during the 1000 days and its systemic impact. Timeline from conception (day -270) to 2 years of age (day +730) with stage coding: prenatal (blue), neonatal (green), infant (yellow), young adult (orange) and geriatric (red). For each stage, salivary parameters (flow, pH, buffer capacity, secretory IgA), dominant microbiota, key antimicrobial peptides and molecular biomarkers (cytokines, microRNAs) are detailed. The lower panel projects long-term systemic risks with OR/HR values derived from meta-analyses. Data synthesized from references 6-29.

4. DISCUSSION

4.1 Mediation Mechanisms: Saliva as Biological Vector

Saliva is not a passive reflection; it functions as an active transmission system through three main pathways:

1. Direct bacterial translocation: Daily swallowing of 500-750 mL saliva introduces 10^{11}-10^{12} bacteria/day to the intestine. In xerostomia, viscosity increases 3×, protecting pathogens from gastric stress and facilitating intestinal colonization[25].

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2. Systemic immunomodulation: Salivary cytokines (IL-6, TNF-a) resistant to oral proteolysis reach portal circulation, activating chronic hepatic inflammatory response. Mouse studies show periodontitis saliva induces hepatic insulin resistance in 14 days26.

3. Salivary epigenetics: P. gingivalis salivary butyrate inhibits HDAC2 in oral and intestinal epithelial cells, hypermethylating tumor suppressor genes (p16, p21) detectable in peripheral blood[27].

4.2 "Programmed Salivary Signature" Hypothesis

We propose that saliva establishes an epigenetic-immune signature in the 1000 days through:

• Cytokine promoter methylation: Neonates exposed to maternal periodontitis show IL-6 promoter hypomethylation in salivary mononuclear cells (methylation difference -12%, p=0.003)[28].

• Exosomal microRNAs: Maternal salivary miR-155 and let-7b are transmitted via milk, regulating neonatal TLR-4 expression29.

• Antimicrobial peptides (AMPs): Umbilical cord salivary a-defensins predict S. mutans colonization at 6 months (OR 0.42 per defensin doubling)[11].

4.3 Saliva-Modulating Interventions: Therapeutic Strategies

Cuadro 3. Estrategias de modulación salival por etapa del desarrollo / Salivary Modulation Strategies by Developmental Stage

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Salivary Modulation Strategies by Developmental Stage

Etapa / Stage	Estrategia terapéutica / Therapeutic Strategy	Mecanismo de acción / Mechanism of Action	Evidencia / Evidence
Prenatal	Tratamiento periodontal materno / Maternal periodontal therapy	↓ Carga de *P. gingivalis* en saliva amniótica / ↓ *P. gingivalis* load in amniotic saliva	Metaanálisis: OR parto pretérmino 0,58[6] / Meta-analysis: preterm birth OR 0.58[6]
Neonatal	Poblado con *S. salivarius* K12 / *S. salivarius* K12 colonization	Producción de bacteriocinas salivales / Salivary bacteriocin production	RCT: ↓ *S. mutans* 50% a 12 meses[12] / RCT: ↓ *S. mutans* 50% at 12 months[12]
Infancia	Xilitol salival (chicles/geles) / Salivary xylitol (gums/gels)	↑ Flujo y pH, inhibición de adhesión / ↑ Flow and pH, adhesion inhibition	Metaanálisis: ↓ Caries 30%[13] / Meta-analysis: ↓ Caries 30%[13]
Adulto	Inhibidores de proteasas salivales / Salivary protease inhibitors	Bloqueo de gingipainas de *P. gingivalis* / Blockade of *P. gingivalis* gingipains	Ensayo fase II: ↓ Inflamación 40%[14] / Phase II trial: ↓ Inflammation 40%[14]
Geriátrico	Sialogogos (pilocaerpina, cevimeline) / Sialogogues (pilocarpine, cevimeline)	Restauración flujo salival >0,3 mL/min / Restoration of salivary flow >0.3 mL/min	RCT: ↓ Neumonía 34%[24] / RCT: ↓ Pneumonia 34%[24]

5. CONCLUSIONS

Saliva is not merely a washing fluid, but a dynamic ecosystem and liquid biomarker that reflects and mediates oral dysbiosis. Its composition during the 1000 days establishes lifelong systemic inflammatory patterns. Early salivary monitoring enables precise interventions that could reduce chronic diseases by 20-35%.

5.1 Implications for Clinical Practice

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1. Universal prenatal screening of maternal salivary CRP could identify 30% of high-risk pregnancies for neonatal dysbiosis.

2. Infant salivary profiling at 12 months predicts caries with AUC 0.85, enabling targeted interventions.

3. Salivary biomarkers (gingipainases, miR-203) could replace invasive markers in cardiovascular risk monitoring.

5.2 Future Research Directions

1. Develop salivary point-of-care devices for real-time pH, buffer and protease measurement.

2. Validate salivary microbial signature as predictor of response to cancer immunotherapy.

3. Explore saliva transplantation (fecal microbiota transplantation-style) to restore oral homeostasis.

6. LIMITATIONS

1. Methodological heterogeneity: Variability in salivary collection techniques (stimulated vs. unstimulated) limits comparability.
2. Causality: Most evidence is observational; randomized controlled trials of early salivary interventions are scarce.
3. Studied populations: Predominance of Caucasian cohorts; validation in diverse populations is needed.

7. DECLARATIONS

Ethics: No approval required as systematic review.

Conflicts of Interest: The author declares no conflicts.

Funding: This work received no specific funding.

Author Contribution: A.R. conceptualized, wrote and reviewed the entire manuscript.

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