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Systematic scoping review of the noma evidence landscape: current knowledge and gaps

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ABSTRACT

Background Noma (cancrum oris) is a severe gangrenous disease of the mouth and oro-facial structures. Noma often affects young children living in extreme poverty, malnutrition and poor sanitation. Gaps remain in understanding its aetiology, pathogenesis, prevention and treatment.

Methods and findings We systematically searched databases for all primary research studies (clinical trials, cohort studies, case–control, cross-sectional, other observational studies, case studies/series) reporting noma patients of any age up to 7 December 2022. The 366 publications (published between 1839 and 2022) included in our scoping review describe 15 082 patients. Although 53 cohort and 29 cross-sectional studies were identified, enrolling 13 489 patients, interventional research remains extremely limited, with only six studies identified (101 patients, range: 7–26) and only one in the past decade, highlighting a critical gap in treatment evaluation. A total of 380 different treatment modalities were described, which underscores lack of a standardised practice. Disease aetiology remains unclear, with 117 microorganisms reported across 113 studies, yet none more consistently linked to noma development. Since 2000, 91.2% of cases have been reported in Sub-Saharan Africa, though occurrences outside the 'noma belt' and into Asia and the Americas suggest a broader risk. The 212 potential risk factors identified in 269 (73.5%) publications reflect substantial heterogeneity, complicating efforts to determine definitive causative factors. Additionally, the inconsistent definition and reporting of noma staging significantly hinder comparability across studies, with wide adoption of the WHO staging classification needed.

Conclusion This comprehensive review of the literature underscores the urgent need for robust, policy-driven research to address the vast knowledge gaps in the physiopathology of noma and the limited evidence currently available to guide therapeutic and preventive policies. Collective action and increased research investment are crucial, especially now that noma is officially recognised as a neglected tropical disease by the WHO.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Noma is a severe, often fatal disease if untreated, which primarily affects malnourished children in areas with poor sanitation and limited healthcare. Recently recognised as a neglected tropical disease (NTD) by the WHO, significant gaps remain in understanding its causes, global burden and effective treatment. This knowledge gap is exacerbated due to under-reporting, as many affected individuals do not reach healthcare in time. As noma faded from the Western world after World War II, it was neglected in research, leaving a large void in scientific attention. In recent decades, increased reports and broader geographic spread emphasise further investigation and resources are needed to combat the disease. No exhaustive synthesis of the noma evidence landscape existed at the inception of this review in 2018, particularly any relating to evidence-based risk factors, microbiology, prevention, treatment or the burden of disease. Since commencing this work, high-quality systematic and scoping reviews on noma have been published, using existing data collected from clinical trials, longitudinal patient observational studies and retrospective studies as their sources.

WHAT THIS STUDY ADDS

⇒ Despite the identification of numerous studies, there remains a lack of evidence-based treatment and management protocols and inconclusive evidence regarding the disease's underlying causes. This review encompasses a broader evidence landscape, including case series and case reports that were excluded in previous reviews, thus providing a comprehensive baseline of all reported risk factors, microbiological findings and treatment modalities. By assembling data across a diverse range of study designs, this work not only underscores the need for a consistent framework for disease stage classification but also offers recommendations to guide the methodology and reporting of future noma research. This research provides a foundation from which future studies can innovate, address existing gaps and contribute to the development of more effective prevention and treatment strategies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The paucity and methodological heterogeneity of high-quality studies mean that caution is needed in interpreting this evidence when designing future evidence-guided strategies and interventions to tackle noma. A WHO expert committee considered this review in its evaluation of noma for recent inclusion on the NTD list. Moreover, this work will support the development of the noma module for the WHO NTD roadmap.

INTRODUCTION

Noma is a rapidly progressive and debilitating gangrenous disease that involves the mouth and oro-facial structures. At present, substantial research gaps remain regarding the aetiology, pathogenesis, disease burden and treatment of noma. Often reported as a polymicrobial infection, noma is commonly observed with multiple concomitant risk factors, including malnutrition, immunosuppression, infectious comorbidities, poor oral hygiene and extreme poverty.[1–3] The evidence, causality and impact of risk factors on the development and progression of noma remain unclear.

The 'noma belt'—an area of Sub-Saharan Africa between Mauritania and Ethiopia—is often considered to be the main location of the disease. However, more recent reports also continue to identify noma cases in other parts of the world.[3–5] High-quality epidemiological data on noma are scarce. There are few and varying primary reports on the incidence and prevalence of noma, with many publications citing outdated secondary sources.[4] Accordingly, the current regional and global burden of noma is unclear.[6]

Noma disproportionately affects the world's poorest and most remote communities and is most common in children younger than 6 years.[7] Left untreated, the case-fatality rate is high, and survivors are often left with severe disfigurement and varying degrees of functional impairment for life, including difficulty in eating and speaking that can have devastating physical, social and psychological effects. However, early diagnosis and treatment with antibiotics, nutritional support and surgical management (eg, wound care, debridement of necrotic areas and sequestrated bone) in preceding and acute stages of noma can reduce case fatality.[8] Yet, detection is difficult because of the disease's elusive pathogenesis, a diagnosis based solely on clinical characteristics, a lack of disease knowledge, its rapid progression, social stigma and, in some areas, inadequate knowledge in healthcare professionals about how to identify the condition. Detection is further hindered by a lack of public awareness of about noma and limited access to healthcare in impoverished and at risk populations.[9–11]

As of December 2023, noma was duly recognised and included in the official list of neglected tropical diseases (NTDs) from the WHO.[12] Acknowledging noma as an NTD is a pivotal step in increasing the attention and resourcing required to eradicate this social and biomedical indicator of extreme poverty and malnutrition affecting the most vulnerable populations.

This study aimed to exhaustively review and synthesise the existing literature to generate an account of the present state of knowledge about various aspects of noma. The primary research objectives were to describe the evidence-based risk factors of noma observed so far and the supporting evidence, to describe the reported prevention and treatment modalities utilised for noma and their outcomes along with the evidence supporting each and to describe the microbiological findings observed so far and the supporting evidence. Secondary objectives of the project included: to identify existing data supporting the modelling and estimation of the global burden of noma along with development of a map depicting the reported cases of noma globally to date.

METHODS

The protocol was prospectively designed and registered in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO 2019 CRD42019124839). The methodology is briefly described below with a detailed methodological approach published separately.[13] There are only two protocol deviations from the published methodology. The first was an unplanned update to the literature, which was conducted in December 2022. Second, due to the extreme heterogeneity of identified literature and inability to pool and synthesise data across studies as originally planned, although the literature search was designed and executed as a systematic review, the resulting synthesis necessitated the review type be changed to a scoping review.

Literature searches were initially conducted from databases inception to 4 March 2019 and updated on 7 December 2022, using the search strategy and information sources detailed below. The following databases were searched: MEDLINE, CAB Abstracts, Embase, Global Health (all via Ovid), Scopus, Web of Science (Core Collection), African Index Medicus; Pascal (French language search); ClinicalTrials.gov and WHO ICTRP. African Journals Online: Health and OpenGrey.eu were searched in 2019. WHO-identified and grey literature were also searched. The searches were not restricted by language of publication; however, only data from English, French and Chinese publications were extracted and analysed. Both English and French search strings were developed. The English search string included the terms 'noma OR cancrum oris OR necrotising ulcerative stomatitis OR necrotising stomatitis OR Gangrenous stomatitis'. The French search string included the terms 'noma OR cancrus oris OR stomatite ulcéro-necrotique OR stomatite nécrosante OR stomatite gangreneuse OR gangrène à fusospirochètes'. Online supplemental SF1 provides the comprehensive strategy, study selection criteria and search string by database. In summary, all

Table 1 Noma studies by disease stage

Noma stage	Definition	Number of studies	Number of patients
1. Acute necrotising gingivitis	Spontaneous bleeding gum, onset of painful ulceration of the gums; ulceration involving one or more interdental papillae, foetid breath or halitosis, excessive salivation.	33	958
2. Oedema stage	Rapid extension of the gingival ulceration and the mucosal tissue, foetid breath or halitosis, facial swelling or oedema, painful cheek, high fever, excessive salivation, mouth soreness, difficulty eating, anorexia, lymphadenopathy	27	33
3. Gangrenous stage	Extensive destruction of intraoral soft and hard tissue; lesion with a well-demarcated perimeter surrounding a blackened necrotic centre, separation of the slough, leaving a hole in the face, often around the cheeks or lips; difficulty eating; rapid perforation of the cheek; exposition of the teeth and denuded bones, progressive drying of the facial gangrene; anorexia; apathy.	57	94
4. Scarring stage	Trismus may occur, depending on the location of the lesions, sequestration of teeth and exposure of bones and beginning of scarring.	3	3
5. Sequelae stage	The child is disfigured. Trismus may occur, depending on the location of the lesions; there is teeth loss, feeding difficulties, speech problems, salivary leak, teeth displacement, dental anarchy, fusion of maxilla and mandible bones, nasal regurgitation.	76	1120
Multiple stages*	Studies were identified as belonging to multiple stages if patients clearly defined or reported to progress from one stage to another. Studies where patients presented in different stages were also categorised as multiple stages.	129	10983
Unclear*	Insufficient information to make a judgement on noma stage.	41	1891

Source: Adapted from WHO 2016.[13]
*Additional stages added for the purposes of categorisation for this systematic review.

publications reporting on patients of any age diagnosed with noma were included. Animal studies and studies in humans dealing with noma-like illness (where explicitly reported or conditions resembling but not noma, eg, noma neonatorum, ecthyma gangrenosum, necrotising fasciitis) were excluded. All primary research studies were eligible including clinical trials, cohort studies, case–control, cross-sectional, other observational studies, case studies and case series.

online supplemental SF2 contains the prepiloted data collection and variable dictionary with all data items extracted, definitions and examples.[14] Data were initially extracted at the publication level for each included study by one reviewer and then cross-checked by at least one other reviewer. Any discrepancies or enquiries were resolved by mutual discussion across the data extraction team or in consultation with an alternative reviewer where necessary. Patients were classed according to the 2016 WHO Noma Disease phases (table 1), where sufficient details were supplied.[15] To aid evidence synthesis, categories for both treatment and risk factors were constructed for data extraction, due to the heterogeneity of reporting and variability in terminology and classifications (see online supplemental SF2 for all definitions). Importantly, all extracted variables and their associated synthesis—regarding reported risk factors, treatment, noma stage and microbiology—are presented at the publication level unless otherwise specified. Due to variations in reporting quality and the absence of individual patient data, it was often not possible to discern whether the described factors or treatments applied to all enrolled patients. Unless noted otherwise, patient numbers represent the total number of enrolled patients in a study and serve as a proxy for potential individual data.

A narrative (descriptive) synthesis was performed owing to the heterogeneous data yielded. R (V.3.6.3, R Foundation, Vienna, Austria) was used for aggregate quantitative synthesis and data visualisation including the estimation of case fatality. In cohort and interventional studies, case fatality was calculated as the total number of deaths out of total enrolled noma patients. Meta-analysis of single proportion was undertaken to estimate case fatality using common effect analysis and additionally random-effect analysis with Hartung-Knapp adjustment.[16 17] The results were presented along with 95% CIs and respective 95% prediction intervals. The Oxford Centre for Evidence-Based Medicine Levels of Evidence was used to assess the level of evidence and quality of individual studies across this review.[18]

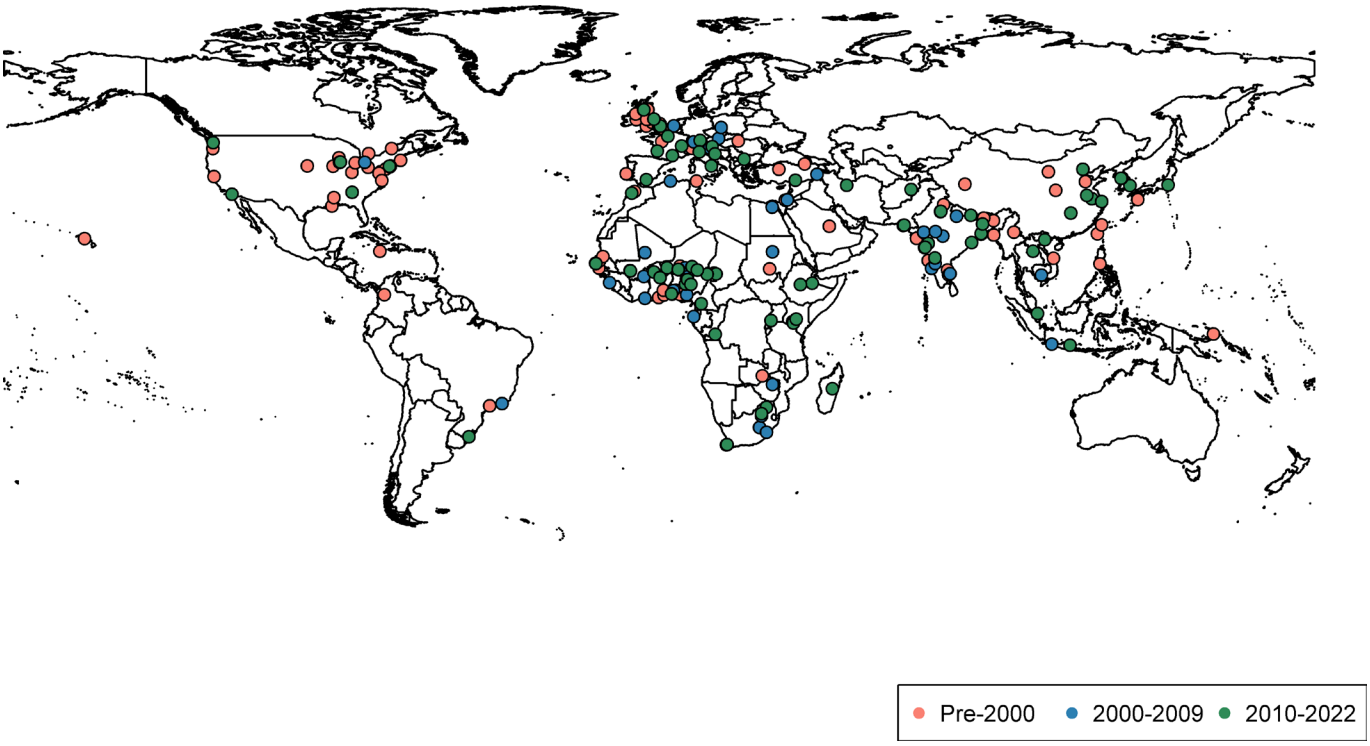

Figure 1 Spatial distribution of all included noma studies. The dots represent the study sites and are not weighted for the number of studies or the number of patients reported.

Patient and public involvement

This scoping review did not involve any direct patient or public participation in the design, conduct, reporting or dissemination of findings.

RESULTS

Study characteristics

From 11 843 records identified across all database and manual searches until December 2022, 4808 unique publications were screened, of which 366 were eligible and included for analysis (PRISMA flow diagram, search results; see online supplemental SF1 and SF2). The 366 publications describe 15 082 noma patients from 69 countries published between 1839 and 2022 (figure 1). More articles reporting noma cases were published since 2001 than in the 50 years from 1951 to 2000. The spatial distribution of studies for various time periods can be found in online supplemental (SF3_Section1a). Country assigned reflects the country setting in which the study was undertaken due to the unclear or inconsistent reporting across the articles with respect to nationality, country of origin or country of residence of included participants. A total of 336 articles (91.8%) did not contain any information on difference between patient origin and study setting or explicitly reported that the patients' nationality and study country were the same. See online supplemental Table 5 SF3 for studies reporting patients of a different origin to study setting. Some of the largest numbers of noma patients per country reported in the included studies were from the 'noma belt' region; Nigeria (n=10 643), Niger (n=887), Burkina Faso (n=580), Ethiopia (n=381) and Senegal (n=324). Limited (Ghana, Mali, Chad, Cameroon, Togo, Benin) or no data (Central African Republic, South Sudan) reported from other 'noma belt' countries.

Of the 366 studies, 86.6% were single-centre studies (n=317), 9.6% multicentre studies (n=35) and unstated for 14 (3.8%). Study designs for the majority of publications were case series/reports (n=270, 73.8%). Only six interventional studies were identified: these included 101 patients, and the number of patients in individual studies ranged from 7 to 26 (table 2). The median number of patients (range) included was 1 for case report/case series (1–69), 40 for cohort studies (2–212), 57 for cross-sectional studies (2–7195), 16 for interventional studies (7–26) and 65 for other study designs (8–296) (figure 2 and online supplemental SF3 Section1d).

Across all study designs, most publications included patients at different disease stages or reported on patients who progressed through more than one noma stage (table 1, online supplemental SF3 Table5). This category of multiple stages was assigned to 129 (35.2%) studies accounting for 10 983 patients. A single noma disease stage could only be assigned to 54% of studies, with the scarring stage under-represented (0.8%). Of publications reporting on patients in a single stage, the most represented was the sequelae stage (20.8%) followed by gangrenous (15.6%), acute necrotising gingivitis (9.0%) and then oedema stage (7.4%).

Risk factors

Risk factors were reported in 269 (73.5%) publications (online supplemental SF3 Table7). Malnutrition and

Table 2 Number of studies and patients by intervention and study design

Intervention	Study design											
	Case series/reports		Cohort		Cross-sectional		Interventional		Other			
	Number of case series/reports	Number of patients†	Number of cohort studies	Number of patients†	Number of cross-sectional studies	Number of patients†	Number of interventional studies	Number of patients†	Number of studies	Number of patients†		
Medical	95	188	6	262	4	157	2	39	1	8		
Surgical	63	426	23	822	3	179	4	62	1	65		
Both	103	244	13	934	3	821	–	–	–	–		
Neither	5	21	7	616	15	1814	–	–	4	214		
Unspecified*	4	5	4	254	4	7630	–	–	2	321		
Total	270	884	53	2888	29	10 601	6	101	8	608		

*Treatment or intervention of any kind was not reported in the publication.
†Total number of patients enrolled in studies which reported use of the intervention. Does not reflect the total number of patients who received the intervention as this was not always discernible or reported for all publications.
Both, medical and surgical; Neither, neither surgical nor medical.

concomitant coinfections appear to be the most frequently reported risk factors (online supplemental (SF3_figure 11)), with no substantial variations in risk factors by geographical region (figure 3). Specifically, 142 (38.8%) studies identified nutritional deficit as a risk factor, 36 (9.8%) did not and 188 (51.4%) did not report nutritional status. Immunosuppression from non-infectious comorbidities was reported in 22.7% of risk factor studies (61/269), including cancer in 25, 12 being leukaemia. Infectious disease (ID) comorbidities were reported in 56.5% (152/269) of publications: measles constituted the main reported ID risk factor (35.5%, 54/152) across all study periods (18 before 1950, 18 between 1951 and 2000 and 17 from 2000 onwards). Other ID risk factors reported across the publications included HIV (14.1%, 38/269), malaria (7.4%, 20/269), tuberculosis (4.5%, 12/269), dysentery (2.6%, 7/269), viral infections (Cytomegalovirus (CMV), Epstein–Barr virus (EBV); 1.5%, 4/269), syphilis (1.5%, 4/269), enteric fevers (1.1%, 3/269), gonorrhoea (1.1%, 3/269), herpes zoster (0.7%, 2/269), visceral leishmaniasis (0.7%, 2/269), poliomyelitis (0.7%, 2/269), meningitis (0.4%, 1/269) and chlamydia (0.4%, 1/269). Unsurprisingly, HIV as a risk factor was most reported after 2000 (32/154 publications during this period) (see online supplemental SF3 section 2b). In 53 (19.7%) papers, unidentified pneumopathies were the most reported respiratory infections (30%). Poor oral hygiene was reported in 28% of publications (75/269). Only 39 (14.5%) publications described possible or likely exposure to physical environment factors (eg, close proximity to livestock, scant sanitation and unsafe drinking water). Socioeconomic factors, namely poverty, were only detailed in 24.2% of the publications (65/269). Lifestyle factors, including smoking, alcoholism and intravenous drug use, were captured in 41 publications, with 51% of these referring to adult patients (21/41). In publications post-2000, nutritional deficit, immunosuppression and IDs remained the leading risk factor categories, accounting for 59.1% (75/127), 29.9% (38/127) and 48.8% (62/127), respectively.

Microbiology

There were 113 (31%) publications reporting microbiological agents or testing. Of these, 78 (69%) identified multiple microorganisms, 20 (18%) a single microorganism and 15 (13%) did not report any specific organism. Information on culture techniques was seldomly reported. Substantial heterogeneity in the variety and level of classification of identified microorganisms (genus vs species) impacted the feasibility of evidence synthesis. A total of 117 different microorganisms (at the family/genus/or species level) were described across these 113 publications. The most frequently documented microorganisms, as per exact taxonomic level reported, included: *Staphylococcus aureus* (22/113, 19%), *Pseudomonas aeruginosa* (20/113, 18%), fusiform bacilli (18/113, 16%), spirochaetes (14/113, 12%), *Fusobacterium necrophorum* (13/113, 11%), *Prevotella*

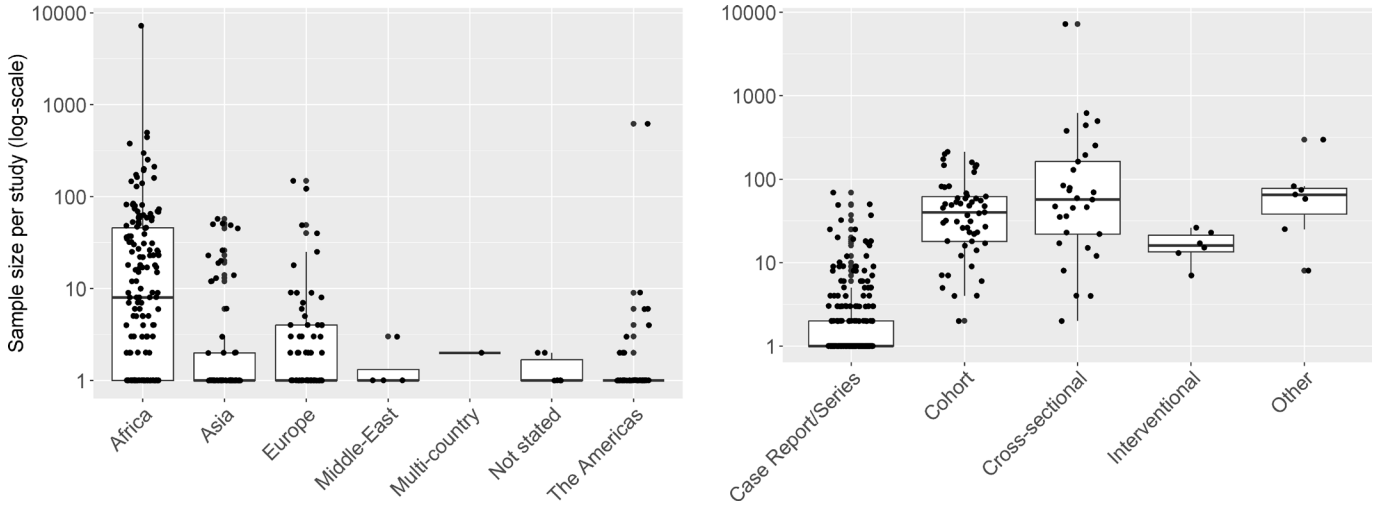

Figure 2 Number of included noma patients (logarithmic scale) per study by (A) region; (B) study design.

genus (13/113, 11%), *Klebsiella pneumoniae* (11/113, 10%), *Peptostreptococcus* genus (8/113, 7%) and *Actinomyces* species (6/113, 5%). One publication could report multiple microbes, so percentages add up to more than 100. More recent case studies reported cultures of resistant organisms.[19–21] A single case from Afghanistan[19] reported multidrug-resistant Escherichia coli prior to any use of antibiotics. One case in South Korea[20] reported identification of a single microorganism, vancomycin-resistance enterococci. Cultures from a case in Mali[21] identified a polymicrobial infection and isolated an Escherichia coli Extended Spectrum Beta Lactamase. Antibiotic therapy was commenced before the microbiological analysis in the South Korea and Mali cases. See online supplemental SF3 section 3 for a comprehensive list of all identified microorganisms as reported and differences observed by region.

Treatment modalities

Most studies (96%, 352/366, n=4207 patients) reported treatment details for noma cases or study population. 30% of studies described medical interventions (108/366), 26% surgical interventions (94/366) and 33% of publications reported both medical and surgical

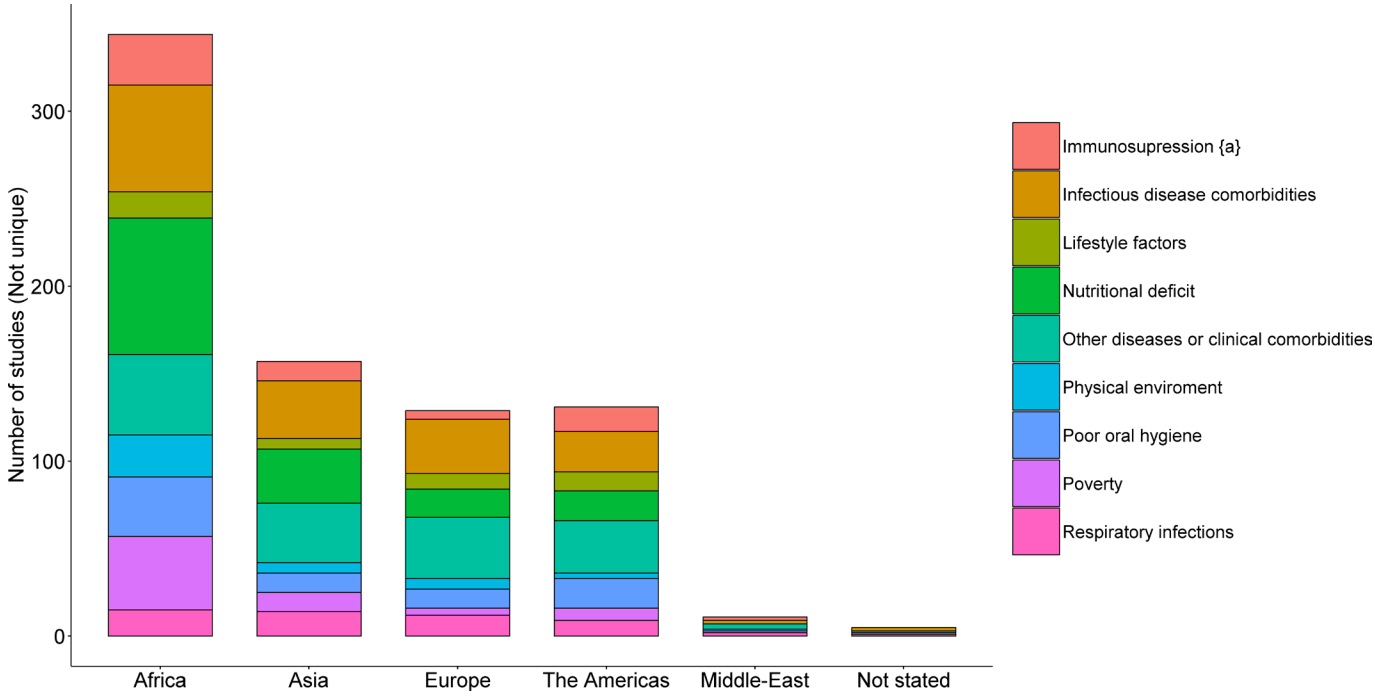

Figure 3 Number of publications reporting risk factor categories by geographical region. The same study might report multiple risk factors and hence the number of studies may sum to >100%. Lifestyle factors included smoking, alcoholism, IV drug use; physical environment included poor living conditions, buildings, sanitation or water supply, close proximity to animals. Definitions of the categorisation of all risk factors are provided in online supplemental file 2. [a]Non-infectious comorbidities causing immunosuppression.

interventions (119/366). A further 8% reported neither medical nor surgical interventions (31/366). The intervention was unknown for a large number of patients (n=8210), though from a limited number of studies in 4% (14/366).

Across 352 studies, 381 different therapeutic interventions were described (online supplemental SF3 table 10). Online supplemental table 13 SF3 depicts the total publications and patients for each of the five subgroup intervention categories. While providing an overview of the reported literature, these results may not align with current intervention proportions. Notably, the majority of included patients received alternative therapies, a result influenced by a single retrospective cross-sectional study of over 7000 patients.[22] In this study, the most common intervention was home treatment with charcoal in 42% of patients (n=3011), followed by 13% (n=951) opting for traditional treatment, including cultural rituals. The majority of publications (n=208, 56.8%) reported other medical interventions and therapies (ie, not antibiotics, see online supplemental figure 1 SF3), which included a wide range of treatments from opiates, tincture of chloride, topical silver nitrate, topical zinc peroxide, vitamin therapy to blood transfusion. Antibiotics (or bactericidal products) were prescribed in 176 studies, only two of which were interventional studies across different noma stages.[23 24] Consequently, there is no evidence to support better results from any antibiotic family (online supplemental SF3 table15 and figure13). Alongside the use of antibiotics in the acute stages, a number of case reports have shown that early intervention, with proper oral hygiene, debridement and chlorhexidine mouthwash, can lead to proper wound healing and no long-term adverse effects.[25–29]

For each study design, the number of patients and studies by intervention category are presented in table 2. Further discussion of noma treatment by study design, noma stage and year of publication, including numbers by additional subgroup intervention categories and detailed observations are provided in online supplemental SF3 section 5. This review found little evidence on noma prevention with no studies examining preventative interventions online supplemental SF3 section 4.

Mortality

Mortality data were reported in 77% of publications (283/366). This included 187 studies explicitly reporting no noma patient fatalities. 291 deaths were reported in 283 publications, with 4181 noma participants. Out of those 291 patients, 88 died from noma's acute effects shortly after admission to a health facility. The remaining 203 stated cause of death was not noma-related. online supplemental SF3 section 6 provides the distribution of death by age, stage and publication period. The median (IQR) case-fatality rate observed from the 37 cohort or interventional studies was 0% (IQR: 0 to 9.7%, range: 0%–83.3%) (online supplemental SF3 figure 21), and the median case-fatality rate was 4.9% (IQR: 2.5% to 7.3%, 0% to 9.7%; range: 0–9.8%) in two studies with stage 1 disease, no deaths were observed in 11 studies reporting stage 5 (341 patients; 0 deaths), 1.8% (IQR: 0%–28.3%, range: 0%–83.3%) in 20 studies reporting multiple stages, and 2.1% (0%–10.3%, range: 0%–28.6%) in four studies with unclear disease stage.

Of the 12 studies that did not use any surgery (facial reconstruction or other forms), the median case-fatality rate was 4.6% (IQR: 0%–28.4%; range: 0%–83.3%), and this was 9.8% in a single study with stage 1 disease, median fatality rate of 3.5% (IQR: 0%–28.3%; range: 0%–83.3%) in nine studies with multiple disease stages, and 14.3% (IQR: 7.1%–21.4%; range: 0%–28.6%) in two studies with unclear disease staging. Using a formal meta-analysis of these 12 studies, the estimate of case fatality was 9.9% (95% CI 7.9% to 12.2%; I^2=87.3%) using a common-effect meta-analysis, and 5.5% (95% CI 0.9% to 26.7%) from random-effects meta-analysis. The estimated 95% prediction interval was wide (0%–94.2%), indicating large heterogeneity of the estimated effect (online supplemental SF3 table 23).

Post-noma complications

Post-noma complications (including traditional orofacial noma sequelae in addition to other physical, mental and emotional complications) were reported in 205/366 (56.0%) articles. Of these, 142/205 (62.3%) publications reported complications related to the facial region, including trismus, sequestration of the jaws, bony ankylosis of temporomandibular joints, severe scarring, fistulisation of cheeks and oro-nasal fistula (online supplemental SF3 section 7).

Burden of disease

Of 366 studies, 118 (32.2%) reported indicators related to the burden of disease: incidence, prevalence, quality-adjusted life years, disability-adjusted life years, financial costs and morbidity or mortality rates. Of 118 publications, only 17 reported primary source estimates (ie, rates or costs calculated directly from primary research reported in the publication). Secondary sources (ie, rates reported as sourced from other literature and not calculated from the primary data) were cited to report the burden of disease in 91 studies. Ten publications cited both primary and secondary source estimates.

Since 2000, studies citing a secondary source of the burden of noma most commonly used WHO's 1998 estimate of global incidence: this was reported in 11 publications, estimating an incidence of 140 000 new cases/year.[30] The latest global estimate was published in 2003. Fieger *et al* reported a lower global incidence of 30 000–40 000 cases/year. Of these, 25 600 cases were expected to originate from Sub-Saharan Africa.[31] Note that this figure was calculated using observed noma patients in northwest Nigeria, then extrapolating to a national incidence before being extrapolated to global incidence. The global prevalence of noma survivors was estimated to be 210 000 worldwide, based on a 15% untreated survival rate and

a life expectancy of 40 years following the disease.[9 32] More recent incidence and prevalence estimates calculated using primary data have been localised to specific geographic regions or territories within the countries of Nigeria, Burkina Faso and one study in Chile (online supplemental (Table 30 and 31 SF2)). However, these estimates vary greatly within and across countries and are discussed further in online supplemental SF3 section 8.

Risk of bias

Of the 366 included studies, one (0.3%) study was graded at level 2 risk of bias, 24 (6.6%) studies were level 3 and the remaining 341 (93.2%) studies were at level 4 risk of bias. No studies were graded to be at level 1 (lowest) or level 5 (highest) studies risk of bias online supplemental SF3.

DISCUSSION

Table 3 summarises the key findings and recommendations of this review, highlighting definable research gaps and offering suggestions regarding future evidence generation required to advance our comprehension of the aetiology, pathogenesis, burden of disease and treatment of noma. The extent of unknowns in these critical areas of disease understanding, coupled with the heterogeneity of the available data, constrained our ability to synthesise the literature, limiting the clarity of guidance beyond what is provided in table 3.

The 366 publications eligible for inclusion represented 15 082 noma cases from 69 countries, published between 1839 and 2022. Research publications on noma increased significantly in the last two decades, in line with the 1994 WHO initiative to launch an international programme to control noma, which increasingly raised the disease profile as a public health issue. However, nearly three-quarters of studies identified were case reports or case series, representing a very low level of evidence for policy guidance. Only six interventional studies enrolling 101 patients (range 7–26 patients) were identified, with only one study from the last decade.

Since 2000, the majority of noma cases have been reported in Africa, but not solely in the historical 'noma belt': cases are also reported in South and South-East Asia, Asia-Pacific and the Middle East. Additionally, there was limited (Ghana, Mali, Chad, Cameroon, Togo, Benin) or no data (Central African Republic, South Sudan) reported from other 'noma belt' countries. This could be explained by the weak health surveillance system in the region and/or lack of reporting of diseases, in addition to limited knowledge of noma among the healthcare providers, primarily due to a lack of exposure in the medical training programmes.[5 10 11] Recent cases reported in Europe and the USA have either been patients imported for surgical reconstruction or, mostly been linked to vulnerable minorities, lower levels of education and oral hygiene practices, cancer and HIV-coinfection.[33 34] Importantly, these countries reflect the country in which the included studies were conducted.

Risk factors

The literature reported 212 different risk factors associated with noma, with IDs detailed in half of them, and measles the most frequently named disease. This corroborates the hypothesis that measles may be an important contributory factor for noma.[35 36] While many noma-affected children are reportedly HIV-seronegative,[37 38] recent studies have also focused on factors associated with HIV infection, which are involved in the development of noma precursors.[39–41] Existing health infrastructure, disease prevention and management programmes for these associated IDs would be paramount in future strategies for effective awareness, early case identification, management and referral for noma.

Chronic malnutrition has commonly been reported in communities affected by noma and may increase susceptibility to infection.[37 42] In over a third of publications, nutritional deficit was described as a risk factor for noma, including wasting, stunting, kwashiorkor, marasmus or a low-protein diet. Reduced immune fitness and disturbed metabolism resulting from present or past malnutrition could play a vital role in both the pathogenesis and progression of noma.[43] The evidence synthesised supports common knowledge that noma manifests itself in settings of severe poverty.[3 44] However, the causality and interdependency of many poverty-associated risk factors could not be accurately teased out, given the level of reporting.

Microbiology

A conservative reading of the results of this review points towards the causative agents of noma being non-specific polymicrobial organisms. Recent publications support this assumption.[45 46] While fusobacteria and spirochaetes are historically reported to be the causative agent of noma, this review aligns with more recent findings that report no clear associations in microbiology analyses, nor noma replication in animal models inoculated with these species.[1 36 45–48] From the 117 microorganisms reported, none appear to be more widespread or uniquely related to the development of noma. The diagnosis of noma, therefore, still remains a clinical one. Without further research, current evidence does not support the development of a definitive technique to diagnose acute noma. The scarcity of information on the aetiopathogenesis of noma, therefore, demands urgent basic science research on the microbiology, pathophysiology, pathobiology and histopathologic features of noma.[1] Techniques required to further investigate the microbiological aspects of noma include more longitudinal sampling in high-risk areas, meta-genomic sequencing, culturomics and host–microbiome interaction studies including aged-matched controls.[49 50] Recent literature also supports our recommendation of using WHO noma staging for any prospective sampling and analysis.[4]

Table 3 Key findings and recommendations

Key findings and research gaps	Recommendations
The number of noma cases reported since 2000 demonstrates the need to reconsider the existing understanding that noma is most prevalent in the 'noma belt' region, with a geographic distribution observed in African countries outside this area and other regions including Asia and the Americas.	Greater surveillance and well-designed epidemiological studies should be conducted globally. Education and awareness efforts of noma, particularly the training of primary care workers and community actors should be expanded globally beyond high-risk countries.
There are large variations across the few reported burden of disease indicators with most estimates extrapolated from retrospective studies, studies with small sample size, and local surveys.	To improve the understanding of the global distribution and burden of noma more robust, population-based epidemiological studies need to extend beyond the 'noma belt' region. Consider promoting systematic reporting at a national level to integrate noma into active surveillance in addition to passive surveillance.
The definition and stages of noma progression are poorly standardised and reported across the literature.	Greater awareness of the WHO's five key stages of noma and use of these criteria in both the case definition and reporting is highly recommended.
There is substantial heterogeneity in the risk factors reported to precede noma. The current level of evidence for these risk factors and often the lack of reporting at the individual patient level limits assessment of their causality and interdependency with the development and progression of noma.	► Risk factors and patient comorbidities should be collected and reported at the individual patient level. New studies should be designed to robustly examine the association between such hypothesised risk factors and noma onset. Appropriate statistical methods should be adopted to adjust for confounding when investigating the relationship between hypothesised risk factor and disease acquisition. ► Discussion within the noma research community on reporting guidance is advised to encourage standardisation and inclusion of details (such as risk factors and patient's country of origin), which are often omitted in prospective publications. More robust reporting alongside the clinical categorisation of patients may assist in providing additional context and data needed to address several noma research questions.
Infectious diseases as a possible risk factor for noma were detailed in 52% of included publications.	Existing health infrastructure, disease prevention and control, vaccination and management programmes for these associated infectious diseases should be considered in future initiatives for effective awareness, case identification, treatment and referral for noma.
Malnutrition was the most frequently reported word across the included publications when examining risk factors.	Community-based screening programmes for noma should be incorporated or aligned with existing infrastructure which targets nutritional status, growth monitoring and intervention.
Paucity of information and limited reporting on the microbiology of noma. The association and role of different microbiology in the development and progression of noma is unclear with 117 different microorganisms observed across reported noma cases.	► Urgent demand for basic science research on the microbiology, pathophysiology, pathobiology and histopathologic features of noma. ► More detailed reporting of the culture techniques and methodologies for identifying microorganisms is needed. ► WHO noma staging should be used for any prospective sampling and analysis to investigate the spectrum of microorganisms at different phases of noma if/when patient progresses through each stage. ► More longitudinal sampling is recommended in high-risk areas in addition to meta-genomic sequencing, culturomics and host-microbiome interaction studies including aged-matched controls.

Continued

Table 3 Continued

Key findings and research gaps	Recommendations
Case reports showed early intervention during the acute necrotising gingivitis stage with proper oral hygiene, debridement, antibiotic therapy and chlorhexidine mouthwash leads to proper wound healing and no long-term adverse effects. However, there are no robust clinical studies assessing the efficacy of preventative interventions.	► Programmes and strategies targeted towards increasing disease knowledge and early diagnosis are key to preventing more severe stage progression. Includes encouraging early reporting and rapid referral. ► Future research including well-designed cohort studies is advised to gain greater evidence in support of recommended preventative interventions. ► Utilising existing health infrastructure, cross-cutting initiatives or routine assessments for the collection of noma epidemiological data, awareness and education.
There are very few high-quality studies which assess treatment modalities for noma. There is wide heterogeneity in modalities reported and insufficient reporting of treatment by disease stage. Even if individual patient data were collected across the included studies describing antibiotic therapy, there is too much heterogeneity in the treatments, dosing regimens and outcome measures to assess the most effective antibiotic treatment protocols.	► Future research should look to more robust study designs, enrolling larger numbers of patients, clearly reporting treatment outcomes by stage of noma. ► Discussion within the noma research community on core outcome measures, treatment protocols by disease stage, minimum and consistent follow-up timepoints and further development of standard case report forms may support prospective data collection conducive to meta-analysis across different research studies.The WHO advice for the early detection and management of noma is recommended until further studies indicate a better approach.[17]
Reported noma case fatality rate has decreased substantially over the last 100 years. However, there is substantial population bias and study design bias (mostly case reports) with most experts conservatively assuming less than 30% of patients affected by noma would reach a care centre.	Community-based surveillance to describe the mortality rate of noma is needed.

Treatment modalities and outcomes

With over 381 different descriptions of noma management reported across 352 publications, the level of evidence for noma treatment was restricted to narrative synthesis. The considerable differences in interventional approaches and methods across observed time periods, study designs and stages of noma prevented meta-analysis, and these variations introduced too much heterogeneity to combine the results meaningfully. Further limiting synthesis, and in the absence of individual patient data, was the inability to confirm that all patients in each study received the described treatment.

Unsurprisingly, antibiotics (most commonly penicillin, metronidazole, clindamycin, streptomycin and ceftriaxone) were the predominant treatment for noma after 1950 once they were widely available.[51–53] Although 176 publications (across all time periods) reported the use of antibiotics (accounting for 2254 patients), the heterogeneity of specific antibiotic(s) used, dosing regimens, treatment assessment and quality of study design prevented further comparisons to support one antibiotic or regimen over another. Only two interventional studies assessed antibiotic therapy for noma management across different noma stages. The current levels of evidence to guide one specific antibiotic treatment regimen over another for noma are, therefore, very weak.

However, the evidence in this review does support expert observation that antibiotics in the acute stages of noma reduce case fatality.[11 39] Due to the polymicrobial nature of noma concomitant infection, broad-spectrum antibiotics should be considered. Currently, the WHO proposes a combination of antibiotics for 14 days, although this is a short antibiotic regimen if the infection is already affecting the bones, where antibiotics should be given for 4–6 weeks.[15 54]

Surgical reconstruction was assessed in four of the six interventional studies, with comparable results demonstrating favourable patient and clinical outcomes, with no serious complications and no deaths.[55–58] Similarly, the most common interventions observed in cohort studies identified in this review were surgical reconstruction of the face in noma survivors, mainly through the use of flaps.[33 59]

In the absence of a clear aetiology and pathogenesis of noma, and with the need to prioritise basic science research, the variety of treatments and lack of standardised approaches to managing noma are likely to proliferate. Future interventional studies on noma should focus on

early detection and prevention, such as community-based screening programmes and nutritional or antimicrobial interventions in high-risk populations. Given the ethical challenges of observing disease progression, studies could also explore biomarkers for early-stage noma, alternative diagnostic tools and strategies to improve access to timely treatment in hard-to-reach areas.

Mortality and post-noma complications

While the mortality rate for untreated patients is reported to be as high as 70%–90%,[11 30] with appropriate treatment, the mortality rate of noma reported in the literature is usually less than 10%.[2 60] Considering the totality of published evidence reviewed, our results support this estimate. Mortality rates are likely to be underestimated, but these rates still make noma one of the deadliest diseases in young populations.

However, serious caution is required in interpreting these results. Most patients across the included studies attended a care facility or hospital and are therefore likely to be unrepresentative of noma cases in the community. Furthermore, many included publications described survivors of noma, with a likelihood of selection bias for surgical rehabilitation studies by expert teams.[2 61]

Although the reported mortality associated with noma has decreased substantially over the last 100 years, the morbidity associated with post-noma complications among survivors has increased the global burden of this disease. Mental health and psychosocial management of patients post-noma is required due to complications, changes in physical appearance, functional debilitation and social stigma, yet such management is severely underreported in the literature included in this review.[62] Facial reconstruction can reduce this burden but often requires multiple surgeries, which are out of reach for the majority of noma patients because of their limited availability and high costs. Given the disease disproportionately affects vulnerable populations and predominately children, stigmatisation and isolation due to post-noma deformity are often in itself a death sentence or for life-long suffering, even when patients survive.

Burden of disease

There are large variations in the quality of evidence provided by primary source estimates of incidence and prevalence reported. Much of the burden of disease data, with similar estimates in two recent reviews,[4 6] is obtained from retrospective hospital records, precluding the robust estimation of incidence. Other studies report noma prevalence from hospital-based or local cross-sectional surveys, which vary greatly within and across countries, or as a complication in cohorts of patients suffering from other IDs. Evidence suggests noma occurs in clusters within countries, meaning cases tend to appear in specific geographic areas or communities and are not evenly distributed. Furthermore, within and across countries, there is significant heterogeneity in the estimated incidence, observed number of reported cases and risk factors that often precede the disease.[4 6 63]

Limitations

The results provide an overview of all treatments described across the literature and cannot be used to estimate the proportion of interventions as used today. Techniques for the culture of microorganisms were not reported consistently or clearly. Where reported, the timing of when samples were collected varied from days to months after the first symptoms, further making comparisons challenging. Therefore, the evidence to support a clear association between noma and any one microorganism is extremely weak. The vast number of proposed risk factors and the heterogeneity of terminologies and categorisation substantially impacted evidence synthesis. Although risk factors captured here have been observed in at least one noma patient, more often, the factors reported related to the collective study population—the prevalence or combination of factors at the individual patient level was not evidenced. Largely due to when they were published, few studies explicitly reported noma stage using the 2016 WHO definitions. In publications where WHO staging was not used, extrapolation of noma phase was attempted, and judgements were made through careful consideration of reported symptoms and diagnosis. Although cross-checking of data extraction was conducted by multiple reviewers, this was not performed blinded introducing potential bias, unintentionally influencing data interpretation and entry. Unless clearly reported or evidenced between conference abstracts and subsequent publications, it was not possible to accurately determine if patients are represented and, therefore, double-counted across publications. The literature is hardly representative of all noma cases, mostly representing those patients who attend healthcare facilities and are subsequently reported—this cohort is conservatively estimated as less than 30% of noma cases.[30] By necessity, there are severe limitations in interpreting and generalising reported deaths and rates of post-noma complications as described above. All results should be interpreted with caution, with these limitations taken into consideration.

CONCLUSION

This scoping review highlights a dearth of high-quality, comprehensive research studies, which extend our understanding of noma aetiology, pathogenesis, prevention and treatment. Limited evidence, therefore, exists to inform future public health programmes and assist the development of effective noma control strategies and interventions. Greater surveillance and well-designed epidemiological studies are required globally. The recent inclusion of noma in the WHO NTD list may help prioritise

urgently needed research to address the many knowledge gaps about this disease, which disproportionately afflicts the poorest in society. In comparison to other NTDs, noma is among the neglected of the neglected.

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