Risk factors for diagnosed Noma in North West Nigeria, 2017

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Sequential Mixed Method Study Protocol

Version 3.0, 1st May 2017

4 List of abbreviations

CI	Confidence Interval
HIV	Human Immunodeficiency Virus
MSF	Médecins Sans Frontières
MUAC	Mid Upper Arm Circumference
OCA	Operational Centre Amsterdam
OR	Odds Ratio
TB	Tuberculosis
UDUTH	Usman Danfodiyo University Teaching Hospital
WHO	World Health Organization

5 Project Information

Draft	1st May 2017
Revisions	Version 3
Study design	Sequential Mixed Methodology Study
Study hypothesis	Patients diagnosed with Noma have identifiable risk factors for the development of disease compared to children of similar sex and ages in their villages of origin
Study period	6 months Proposed Start Date – January 2017
Study site	Sokoto, Nigeria
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Data collection and analysis by	MSF OCA
Collaborating institutions	Usman Danfodiyo University Teaching Hospital (UDUTH) Health Research and Ethics Committee University of Cape Town

6 Summary

Background

Noma is an orofacial gangrene that rapidly eats away at the hard and soft tissue as well as the bones in the face. Noma has a 90% mortality rate, and the disease affects mostly children under the age of 5. Little is known about Noma as the majority of cases live in underserved, difficult to reach locations. MSF runs projects at the Noma Children's Hospital in Sokoto, northern Nigeria and currently assists with surgical interventions for the patients who have survived and sought care at the hospital. Community outreach and active case finding are also taking place. These projects place MSF in a unique position to study Noma, and to add to the scant body of knowledge around the disease.

Aims and objectives

Aim

To identify risk factors for Noma in north west Nigeria in terms of epidemiological (demographic characteristics, medical history), socio-economic-behavioural aspects and access to health care in order to better guide existing prevention strategies.

Specific objectives

1. To understand concepts and perceptions of Noma within the population of northwestern Nigeria, specifically those affected (caretakers of Noma cases) by the disease, and controls matching these cases. To describe the epidemiological profile of all cases of Noma that have been treated at the MSF Noma Children's Hospital from August 2015 until June 2016;
2. To describe the current Noma patient's clinical history before the onset of the disease, the start of the disease and the care/treatment sought as well as the impact of Noma on the patient;
3. To assess Noma risk factors by comparing cases enrolled at the Noma Children's Hospital and controls matched to cases by sex, age, and village of residence;

All of these objectives are in order to assess if there are intervention opportunities in the unique Nigerian setting that could prevent further Noma case development.

Methods

1) **Qualitative phase:** focus groups will take place with care takers (guardians or parents) of cases as well as key informant interviews with health care workers to better understand the local concepts, vocabulary and expressions used to describe Noma in this part of Nigeria.
2) **Descriptive epidemiology:** description of all available medical, nutritional and mental health data associated with the Noma patients operated on at the Noma Children's Hospital over the last year.
3) **Case control study:** assessing risk factors for Noma using care takers of cases recruited from the Noma Children's Hospital and care takers of controls that are recruited from cases village of residence and matched by age and sex.

Outcomes

- Initiate the MSF operational research agenda around Noma in Nigeria;
- Improved understanding of local beliefs, traditions and language used to describe Noma;
- Improved understanding of Noma patients at the Sokoto Children's hospital;

- Identification of preventable risk factors for Noma development in our patients;
- Integration of information obtained into outreach programming, improved community engagements, options for preventative campaigns and overall improved clinical and mental health care of Noma patients and caretakers in the MSF project.

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7 Background

Introduction

Noma, also known as cancrum oris , necrotising ulcerative stomatitis or orofacial gangrene , is a gangrenous bacterial infection of the oral cavity which causes widespread local destruction, disfigurement and disability . Noma was first reported by Hippocrates in the 5th century BC and the disease became a World Health Organization (WHO) priority in 1994 .

Noma starts as an inflammation invading the jaw, lip, cheek and nose which quickly leads to gangrene . Soft tissues and bone are rapidly destroyed, and the mortality rate of the disease in children is reported to be 90% when left untreated . The destruction of hard and soft tissues can be attributed to “immunopathological response to microbial factors rather than microbiological factors alone” . If the tissues heal, it does so as scar tissue which replaces the muscle .

The true cause of Noma is unknown but it is considered to be a mix of factors that contribute to its development (poverty, malnutrition, poor oral hygiene and a recent infection of an infectious disease) . It is believed that poor oral hygiene can lead to the development of ulcers which act as an entry point for microorganisms which cause the disease to develop. The progression of Noma is very rapid, and death can occur within a few days of onset . Stigma and social exclusion are other side effects of Noma, 56% of patients who sought treatment at the MSF Noma program due to stigmatisation (unpublished data from the MSF Noma Children’s Hospital in Sokoto).

Treatment options for Noma are limited, Noma has an active stage and an inactive stage, during the active stage, little can be done besides wound care, and once Noma becomes inactive, only extensive reconstructive surgery can assist patients regain normal functionality, and these interventions are only for the reported 10% who survive and prior to surgery, the patient’s nutritional status needs to be assessed and improved if necessary. Surgical treatment is most effective once the infectious period is over and Noma is inactive . Surgical treatment has been conducted with differing results, Zimbabwe based study showed satisfactory results, but long term follow up was not possible as all patients were lost to follow up within 12 months . Long term effectiveness of trismus release surgical treatments were seen as poor in one study conducted in Sokoto, north west Nigeria, with only 39% of patients showing improvement .

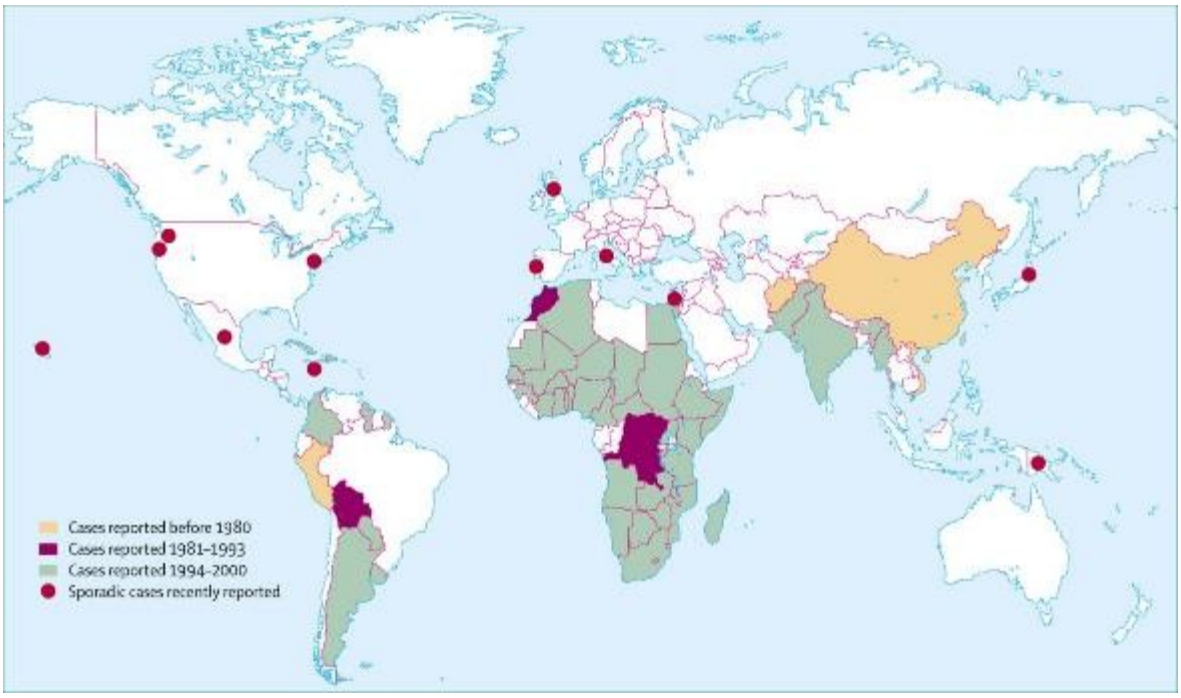
It is challenging to accurately estimate the current global prevalence and incidence of Noma due to the high mortality rate, isolation of patients, remote location of cases and difficulties with follow-up of patients . One study estimated the global prevalence of Noma to be between 30 000 and 140 000 cases , while the WHO estimates a global incidence of 140 000 per year . .

4.1 Distribution and Risk Factors

The majority of Noma cases are reported on the so-called Noma belt along the Sahara which stretches from Senegal to Ethiopia . Cases have been reported from other parts of the world including one case report in an Afghan child and an immunosuppressed elderly man based in the United States . Noma was widely spread throughout Europe, but had mostly disappeared by the end of the 19th century. There was a resurgence of cases during World War II in the concentration camps in Europe, attributed to the poor oral hygiene and

nutritional status of prisoners in the camps . Currently, Noma is only seen in the Southern hemisphere (Figure 1). However, very little evidence around the precise risk factors for the disease exists.

Figure 1: Global Distribution of Reported Noma Cases



Noma is most prevalent amongst the poorest populations in low socio-economic settings , and occurs mainly in children from the ages of 2 to 5 years . However, in rare cases, some patients survive with Noma into adulthood. Noma typifies the complex interactions between extreme poverty, severe malnutrition, unsafe drinking water, poor sanitation, poor oral hygiene practices, high infant mortality, limited access to high quality health care, low childhood vaccination rates and intrauterine growth retardation . Recently, an increased incidence of Noma has been reported in patients with Human Immunodeficiency Virus (HIV) .

Further observational studies around Noma have suggested that additional risk factors for Noma development include: stunting from malnutrition, low birthweight, absence of breastfeeding, co-morbidities and proximity of livestock to area of residence . A recent risk factor study with patients in Niger identified similar risk factors, most notably: stunting and wasting, number of mother's past pregnancies and disease in previous 3 months . Evidence from a Zambian based study corroborated some of these points, indicating that dietary habits, pre-existing illness and malnutrition are all risk factors. This study showed a high proportion of Noma cases were in children aged 1 – 3 years, and, as the investigators noted that this was the stage when the majority of patients changed from breast-feeding to solid feeding (a process called weaning), nutritional deficiencies in the solid food were noted as potential risk factors. Seasonal influences were also seen to have an impact on case numbers (rainy season had the majority of cases) . A contradictory study showed that the majority of cases occurred in the dry season, when food was scarce . One unique risk factor identified in northern Nigeria is a lack of maternal care as mothers may leave babies with grandparents as the mother needs to work. The grandparents then take control of feeding,

and children are sometimes given alternative nutrition such as tea and powdered milk. This practice was apparent in the cases in the referenced study, and the practice identified led to malnutrition .

4.2 Occurrence in Nigeria

The incidence of Noma in north west Nigeria is estimated to be 6.4 cases per 1,000 children in the general population , with Sokoto, Zamfara and Niger states accounting for over 70% of cases, the other 30% of cases come from a range of locations in the region (unpublished data from the MSF Noma Children's Hospital).

In Hausa, the most commonly used (but not only) language in northern Nigeria, there is no specific name for Noma, but the term 'ciwon iska', 'the disease of the wind' is used to describe this and other facial disfigurements such as cleft .

4.3 Médecins Sans Frontières project

The Noma Children's Hospital in Sokoto (Figure 2 and 3) has been providing treatment for Noma patients for many years, and, since 2015, Médecins Sans Frontières (MSF) Operational Centre Amsterdam (OCA) has supported Noma initiatives at the hospital. Between August 2015 and August 2016, four surgical 'sessions' (lasting approximately two weeks) have taken place treating 94 Noma patients in total. Upon admission, the majority of these patients were between 0 and 4 years of age (n=40, 43%), followed by 5 – 14 year olds (n=22, 23%). Ninety-five per cent of these cases were Hausa, and there was an even distribution of males and females. Seventy-three per cent of cases had not received treatment prior to that made available at the MSF Noma Children's Hospital. The main reason for cases presenting were reported to be cosmetic (n=55; 59%), stigmatization (n=55; 59%), in order to improve functional disability (n=31; 33%) and other reasons (n=13; 14%). The majority of care givers reported occupations of either farming (n= 12; 13%) or housekeeping (n = 31; 33%), and anecdotally many care givers stated that a lot of their time was taken up by caring for the patient. Sixty-eight per cent of cases reported they had received Arabic education, while a small percentage of others reported primary (2%) and secondary school (1%). Seventy-seven cases had malaria, seven had other diseases (none reported having HIV or Tuberculosis) and fifteen were malnourished. Ninety-two patients underwent surgical reconstruction, the majority of which included a deltopectorial flap, an estander flap and the release of the trismus. Eighty-eight surgeries were performed under general anesthesia and seven under local anesthesia. There is no information currently about the post-operative complication rate, the dehiscence or the improvement of mouth opening but three cases of flap necrosis were reported (20%, 50% and 100% necrosis respectively).

MSF-OCA in Sokoto is perfectly positioned to add to the body of knowledge around Noma, as they are currently running surgical programs with patients at the Noma Children's Hospital in one of the most regions most highly impacted by Noma. By conducting this research, important questions can be answered which will guide program planning and resource allocation of intervention programs.

Figure 2: Sokoto State in Nigeria (indicated in red)

Source: https://en.wikipedia.org/wiki/Sokoto_State#/media/File:Nigeria_Sokoto_State_map.png

Figure 3: MSF Noma Childrens Hospital

4.4 Justification of this study

Many aspects of Noma infection remain unknown, such as risk factors for acquiring Noma, what favours survival and what risks are associated with poor outcomes. This proposed study would therefore add much needed information to a scant body of evidence around this disease in order to better understand the disease and so morbidity and mortality due to Noma as well as surgical complications can be minimized, better case finding can be conducted and effective awareness and prevention programs can be organized. MSF is eager to contribute to the evidence around Noma and the programme running at the Noma Children's Hospital in Sokoto places them in a unique position to do so. This study will also be used as a base for the development of a comprehensive operational research approach and effective program planning around Noma in north west Nigeria.

8 Aims and objectives

9

8.1 Aim

To identify risk factors for Noma in north west Nigeria in terms of epidemiological (demographic characteristics, medical history), socio-economic-behavioural aspects and access to health care in order to better guide existing prevention strategies.

8.2 Specific objectives

1. To understand concepts and perceptions of Noma within the population of northwestern Nigeria, specifically those affected (caretakers of Noma cases) by the disease, and controls matching these cases.
2. To describe the epidemiological profile of all cases of Noma that have been treated at the MSF Noma Children's Hospital since from August 2015 until June 2016;
3. To describe the current Noma patient's clinical history before the onset of the disease, the start of the disease and the care/treatment sought as well as the impact of Noma on the patient;

4. To assess Noma risk factors by comparing cases enrolled at the Noma Children's Hospital and controls matched to cases by sex, age, and village of residence;

All of these objectives are in order to assess if there are intervention opportunities in the unique Nigerian setting that could prevent further Noma case development.

9 Methods

9.1 Study design

This study will comprise sequentially of three phases, caretakers mentioned in these phases refer to parents or guardians of Noma cases or controls:

1) **Qualitative phase:** In order to better understand local concepts and how families that have experienced Noma and practitioners that treat Noma perceive the disease, we will gather information using qualitative exploratory methods. The local vocabulary and expressions used to describe Noma from this part of Nigeria, as well as the beliefs around the disease will inform the second and third phase of the study;
2) **Descriptive study**: analysis and description of all available medical, nutritional and mental health data associated with the Noma patients operated on at the Noma Children's Hospital over the last year, to have a comprehensive epidemiological description (time, place, person) of the cases seen to date;
3) **Analytical study**: implementation of a case-control study with a sub-set of Noma patients (as cases) and matched controls to fulfill the main objective of the study.

Each of the phases is described below.

9.2 Phase 1: Qualitative

A qualitative, descriptive research design will be used due to the exploratory nature of the subject. It will be conducted using key informant interviews and focus group discussions. The aim of these will be to better understand the concepts, perceptions and understanding of Noma in the Sokoto community, identify some key terms in Hausa that are commonly used to describe Noma, what respondents think causes and prevents Noma, and the cultural beliefs surrounding the presentation of Noma. Results from the qualitative work will assist in gaining a deeper understanding of Noma, which will assist the approach to Noma care.

9.2.1 Sampling and recruitment strategy:

Focus Group Discussions

Five focus group discussions will be held with caretakers of current Noma patients that are enrolled at the MSF Noma Children's Hospital. Focus Groups will be composed of not more than 8 participants at a time. Purposeful sampling will be applied and the groups will be divided by sex to alleviate any discomfort participants may find discussing these issues in front of a person from another sex, due to the strict cultural separation norms of this region, a homogeneous group will be more informative. The head matron acting as gate keeper will invite care takers to volunteer to participate. The selection will be convenience based sampling but the matron will try to ensure there is a variety of demographic characteristics being represented including those from rural and urban areas. The focus groups will be organised and conducted sensitively in a private neutral location where participants hold their regular meetings to optimise comfort and privacy within the group. This will enable a space for explanation and dialogue to speak about the purpose of the research and allow for

potential sensitivities to be addressed. Through the use of vignettes participant reflections on relevant life memories and current experiences related to Noma will be explored.

Full information about the purpose and uses of participants' contributions as well as clarification of how contributions will be shared will be explained during the informed consent process (Annex 1c). Participants need to be encouraged to keep confidential what they hear during the focus group and be reassured that data from the group will be anonymised using pseudonyms with care taken for quotes not to be traced back to individuals by the researcher.

Inclusion is voluntary and inclusion criteria for focus groups are: (i) caretaker of Noma patient enrolled at Noma Children's Hospital, (ii) over the age of 18 years, (iii) case under the age of 15 when Noma was contracted (iv) willing to participate in the focus group.

Key Informant Interviews

Purposeful sampling will be applied for the key informant interviews; the researcher will actively select 12 medical staff at the MSF Noma Children's Hospital informants that are seen to be most likely to provide insightful knowledge. The final number of participants will only be known when data saturation occurs, but similar studies have established a sample size of 12 interviews as a working figure for homogenous group selection . Snowball sampling will support this, where subjects may recommend further potential candidates to the researcher. This is thought to be appropriate in the context, as medical staff at the hospital are likely to know of each other and would be able to suggest the most beneficial people to interview. Key informant interviews will be conducted in a private venues suitable for the interviewee/s, by the field researcher, who will supervise a trained translator for non-English speaking participants.

An open ended question approach, detailed in Annex 4, will be used. Key informant interviews will focus on the perceptions and experience around Noma in caring for Noma patients at Noma Children's Hospital. This might also touch on healthcare staff's personal beliefs around the disease and its clinical evolution. Inclusion is voluntary, and inclusion criteria for key information interviews are: (i) health care worker at the Noma Children's Hospital, (ii) over the age of 18 years, (iii) willing to participate in the focus group. Exclusion will include (i) those not consenting to participate and (ii) participants to unwell to participate.

All key informant interviews and focus group discussions will be recorded verbatim with informed voluntary consent (Annex 1c and 1d).

9.2.2 Data Collection, Protection and Analysis

The Key Informant Interview Guide along with the Focus Group Discussion Guide are attached in Annex 4 and 5.

Interview Language

Two possible methods will be used for the Focus Group Discussions. The first would be for the Field Researcher to lead the focus group discussions, through the aid of a translator. Discussions would be recorded, transcribed into Hausa and then translated into English. We acknowledge the limitations of this method. The second method would be to train a Hausa speaking research assistant who would conduct the focus group discussions which would be recorded. The assistant would then transcribe the interviews

into Hausa, and they would then be translated into English. The researcher will use their discretion on which method to implement.

Key Informant Interviews will be conducted by the Field Researcher with assistance from a translator if necessary. The interviews will be recorded and fully transcribed. If the interviews are conducted with assistance from a translator, then the interviews will be transcribed into Hausa and then translated into English. The translator will be trained and supervised by going over the study methodology and all questions will thoroughly be examined, any issues around content will be discussed and resolved, including informing on local idioms that will help better understand the translating. A terms of reference will include respect towards all parties involved in the study; maintenance of confidentiality and accuracy when translating; confirming no conflict of. A confidentially agreement will be signed by the translator.

Analysis

Data Analysis will be run concurrently to inform probing with subsequent interviews. We will use grounded theory approach, so that emergent codes, patterns and themes are based in the data derived from interviews and FGDs and checked with reflexive practice to ensure against the insertion of preconceived assumptions. An inductive process of developing theory or concepts emerging from participant accounts as well as exploring and testing pre-existing ideas will be used. Participant responses from key informant interviews will be compared with other data sources, such as FGDs where convergent themes will be identified. In this way we will be looking for points of agreement or difference between the perspectives and accounts drawn from the interviews and group discussions; i.e. are the names used for Noma the same between patient groups, and between key informant health care workers and patients. Selected anonymised narratives or case studies will be drawn out to ensure the individual ‘stories’ are not lost and to explore how the themes interrelate in particular cases. The text generated from focus groups may enrich or add to deeper understanding provided by individual interviews. Data with be sorted and organized using Nvivo 11. We will compare emergent themes and findings to other studies through a secondary literature review.

The qualitative findings will be analysed for divergence or tensions with quantitative data, adding depth to some sections of exploration, such as the concepts used to describe Noma which is in both the quantitative and qualitative research sections. We may find an emergent theme in one data set which is present in others which will be explored as a thematic thread and analysed further to generate an integrated account for a richer understanding of Noma. We will link this back to the wider research question.

Data Validation:

Data is being collected from a variety of sources in order to compare and strengthen related conclusions. Data checking will be conducted through respondent validation at the end of each interview and focus group, as well as doing repeat transcriptions on 10% of transcripts to ensure validity. Deviating cases and testing emerging theories with be included, instead of only selecting examples which reiterate desirable points (Green & Thorogood, 2009). For bias reflection of the role of the researcher as a confounding factor will be considered throughout the analysis, with documentation of research process to facilitate a clear account of procedures used as an audit trail that can be easily followed. *Data Protection*

A confidentiality agreement will be signed with the translator to ensure privacy and confidentiality. Audio recordings will be destroyed once transcription has been completed. Transcription and translated documents will be coded by participant numbers, no identifying data will be kept on transcriptions. These transcriptions will be kept in a password protected file, only accessible to research staff, electronic data will be deleted and paper copies will be shredded after 5 years.

9.3 Phase 2: Descriptive study

9.3.1 Study population

We aim to conduct an overall description of all Noma cases that were enrolled at the Noma Children's Hospital since August 2015 and thus will include all patients that were assigned an MSF admission number since that time.

9.3.2 Sample size

For the overall description we will include all cases enrolled in the program since August 2015.

9.3.3 Data collection

We will rely on routinely collected medical, nutritional and mental health data as part of the surgical program. This data will be available in the mental health data tool, the nutritional data tool as well as the Noma data tool. The mental health data tool records data on individual counseling and group counseling sessions attended by each of the Noma patients enrolled in this part of the programme. The nutritional data tool monitors (in aggregate) the numbers of patients enrolled in the nutritional programme, their overall entrance criteria (based on mid-upper arm circumference, Weight for Height measurements or bilateral oedema) and the overall exit criteria. The Noma database was specifically designed for the Noma project in Sokoto. It aims to track the medical presentation and general medical evolution of each Noma patient in the project from the time of enrollment to their discharge of the programme. Thus it records the status of the Noma upon enrollment, the operations and procedures undertaken to treat the disease, complications arising from anesthesia or infection, any laboratory results obtained and nutritional status measurements throughout their duration in the programme). Records will be accessed retrospectively for this part of the study.

9.3.4 Data entry

For the overall descriptive data, all records from the above-mentioned data tools will be exported into a format that can be imported into STATA 14.

9.3.5 Data analysis

Medical programmatic data will be analyzed in terms of epidemiological and clinical information to determine frequencies and proportions of different variables: age distribution, sex, area of residence, time of onset, previous clinical history, grading of Noma at start of program, operations sustained during program admission, outcome of operations, nutritional status prior to admission, during admission and upon discharge and mental health outcomes. Analyses will be performed using STATA 14.

9.3.6 Data management

All line-listed medical data tools are protected with a password and all aggregate data tools are open access. Data will be extracted from these data tools and all individual identifiers will

be removed (i.e. name of patient, name of caretakers etc.), thus all analyzed data will be anonymous and will no longer be linked to individual patients. The PI and Study Researcher will have access to the password, the anonymization will be done by the Study Researcher.

9.4 Phase 3: Analytical study

9.4.1 Study population

Cases will be caretakers of Noma patients under the care of MSF Noma Children's Hospital (either through inpatient services or active attendance through outpatient services) that were<15 years of age at onset of the disease. Controls will be matched by being selected from the same village as the Noma patient (if security permits) and by current age (+/- 2 years) and sex. In the event that the security situation does not allow easy movements to villages of cases, controls may be selected from a MSF feeding center near Sokoto, controls will then also be matched by age.

9.4.2 Sample size

We used the following assumptions to calculate the minimum sample size required to show a true difference in the odds of exposure in cases compared to the odds of exposure in controls for any of the risk factors under study:

- 95% confidence intervals
- 80% power of detection of a true difference
- Ratio of controls to cases: 3
- Expected exposure of the risk factors in the controls of 60%
- Lowest odds ratio to be detected of 2.5

Therefore, if we can include as a minimum 67 cases and 200 controls we will have a sample size large enough to detect odds ratios of 2.5 for our selected risk factors. We will aim to include all current Noma cases in the program at the time of the study.

9.4.3 Sampling and Recruitment Strategy

We will aim to include all Noma patients who have been enrolled in the programme at MSF Noma Children's Hospital in the last 12 months. We assume that there will be an approximately 70 cases available (estimated based on the fact that 94 cases have been seen in the 12 months prior to the inception of this project). Taking into consideration a possible 33% response refusal in control households to participate, we would aim to recruit 280 controls. It is possible that the final number of cases we include (and controls) is larger than the proposed sample size thus increasing our power to identify a difference between cases and controls.

Recruitment of cases will take place at MSF Noma Children's Hospital where inpatients with Noma are staying awaiting treatment by MSF. The investigators will make a judgement call, together with the Medical Focal Point for the Noma project on which patients are considered too ill to request their caretakers/parents to participate in the study. Outpatients known to the team will be contacted and asked to come to the hospital if convenient to participate in the study, if outpatients live too far away, the team will go to where they are located (if security situation permits) to conduct the questionnaire for the survey with them.

Control selection will be done in the matched villages of the cases. Before identifying or approaching potential care takers of controls, the study will be discussed with village leaders, and permission to conduct the study in the villages will be requested. Controls will

be selected if they have no apparent morbidity that resembles Noma. Control selection in the villages will be done by visiting the village of identified Noma cases and after requesting permission from the village elders. Community leaders will be approached and asked for a list of children who live in the village and the ages of these children. A random number table will then be used to select the controls. We will then approach the caretakers of these children to ask if they would be willing to be a part of the study. The informed consent process will follow. If such a list of children does not exist, we will do the control selection through neighboring households of the household in which the cases and their families live.

In the event that security conditions in Sokoto do not allow for travelling to case villages, we will explore the possibility to include children in the MSF therapeutic feeding activities in north west Nigeria (Anka, Zamfara etc.) as controls. Controls will be matched in terms of sex and age (+/- 2 years). We recognize that village-specific exposures using this control group will not be controlled for, but accept this as a limitation for the present research.

9.4.4 Questionnaire

Caretakers of cases and controls will be asked to respond to an interview using a structured questionnaire. The questionnaire will cover the following aspects:

- Socio-demographic characteristics of the household
- Living conditions of the household
- Vaccination status of the child in question at the time of the interview
- Breastfeeding practices of the mother for the child in question
- Child's health and access to care for disease in the child in question (apart from Noma) in the 12 months prior to the interview
- Access to health care in a general way
- Child's oral health
- MUAC measurement at the time of the interview

We will also ask caretakers of Noma cases to provide some more detailed information on their perception of the disease and the impact it is having on their child. Additionally, we will ask these caretakers specific questions around the healthcare they sought for the child when the Noma first appeared (this information is not available in the current medical data from the project).

For caretakers of the controls we will ask them several questions about Noma, how they perceive it, what they think causes it and whether they know anyone in their village that they think has Noma. This last question is not for the study questions to be answered, but opportunistic in the active case finding the Noma project has established in Sokoto for new cases.

All MUAC measurements will be done by the trained study interviewers.

9.4.5 Data Collection

The questionnaires will be applied by interviewing the main caretaker of the child and will be administered by a trained MSF staff member in Hausa, who will also administer the MUAC measurement tool. Staff will be trained in how to use the MUAC tool prior to implementation of the project.

The questionnaires will be translated into Hausa, and then back translated in to English to ensure consistency of language. Information from the pre-study qualitative work will be used

to better adapt the questions in Hausa to match the local way in which the disease is described.

The translated questionnaire will be piloted with three volunteer guardian's/care takers at MSF Noma Children's Hospital in order to check the understanding and appropriateness of questions. Necessary changes will then be made to the questionnaire. These three pre-test candidates will still be voluntarily included in the case control study, if they are willing.

Both questionnaires will be either printed and data collected by hand or they will be formatted to be used on mobile phones or tablets for electronic data collection (to be decided at a later stage as this depends on IT infrastructure in the project location).

The questionnaire for cases is available in Annex 2 in English. The questionnaire for controls is available in Annex 3 in English.

9.4.6 Data entry

In the event we use paper questionnaires to collect data, an Epi Data entry mask will be prepared and all data from paper questionnaires will be entered into this password protected file by a trained Data Entry clerk.

In the event we use tablets for data collection, a specific formatted questionnaire will be uploaded onto the tablet using the software of choice (ODK, Dharma or similar, but to be determined based on MSF-OCA guidelines at the time of implementation). Each time the tablets connect to an MSF –wireless network, they will automatically upload the collected data on the tablet to a secure server (and be deleted from the tablet at the same time). The server is password protected and will only be accessible by the Study Researcher and the Primary Investigator.

9.4.7 Data analysis

Data cleaning and analysis will be done with STATA 14. The single and multivariable analysis will be conducted using conditional logistic regression. Frequencies of exposure to each of the common risk factors included in the questionnaires for cases and controls will be calculated. The odds of exposure to those individual risk factors will be calculated in cases and in controls separately and concurrent odds ratios (ORs) for these with their respective 95% confidence intervals (95%CI) will be calculated.

Depending on the outcomes of the unadjusted analysis we will select those exposures that appear to have an association with the presence of Noma from the unadjusted analysis as well as other variables which we might consider to be confounders in the associations demonstrated in the unadjusted analysis (i.e. age) and include them in a multivariable logistic regression model. The results of this model will include adjusted ORs and respective 95% CI. The impact of effect modification will also be explored for certain exposures.

Finally, we will classify the results specifically to look at possible intervention/prevention opportunities for MSF in the future of the Noma project in Sokoto. For example, if we realise that absence of breastfeeding was significantly associated with Noma, MSF could explore either including breastfeeding health messages in their existing outreach activities or identifying partner organisations who could include such messages in their activities.

9.4.8 Data protection and management

All data including names of patients, caretakers and their contact details will remain anonymous and will only be available in a password protected database at the Sokoto project base to which only certain authorized staff will have access. If paper data collection forms are used, we will ensure that only unique identification numbers are used on the paper format to identify the patients and their respective controls. The key to this information will be maintained by the MSF research staff in a separate password protected database. Extracted data will identify individuals only by the Patient Identification Number, no identifying markers will be on the surveys. Although the results of this study may be published, no information that could identify any of the participants will be included. All reports and publications will refer only to anonymous or aggregated data. Nominal data will not be distributed outside the study location or appear in any report or publication.

If data collection is completed in paper format, the data collection forms will be stored in a locked cupboard within the MSF Sokoto project. Upon completion of the study all paper forms will be stored at the MSF capital office for a duration of 5 years' after which they will be destroyed. If data collection is done using tablets, questionnaires and data will be uploaded each day onto a secure MSF intranet server which can only be accessed by authorized individuals. All surveys will be automatically deleted from the tablets after their uploading to the server. All tablets will be password protected and only interview staff will have access to those passwords.

Confidentiality is paramount, and no information about individual participants or their household members will be accessible to any individuals not directly involved in data entry. Participant identifiers will not be included in results and disseminated reports. The research team will be required to sign a non-disclosure and privacy form stating that they will not discuss information about individuals participating in the study outside of the research team. The research team will ensure the ethical principles of beneficence, non-maleficence, justice, autonomy and respect of persons are adhered to throughout the study.

All data collected is owned by MSF OCA and MSF Nigeria, but is open source and can be requested at any time following the study's completion for additional research or study questions.

9.5 Quality assurance

During the field work, supervision of field teams will be ensured by the Study Researcher, the Mission Epidemiologist and the MoH Co-investigator. All data collection forms will be checked by one supervisor at the end of each study day to ensure that there is no missing or unclear data.

Finally, if data collection is done on paper, after all the data entry has been completed; the Study Researcher will review 20% of all questionnaires at random and compare them to the original paper format to ensure that the data quality is of sufficient quality.

9.6 Informed Consent

In order to ensure each participant provides informed consent, and in recognition of low literacy levels, for participants ≥18 years of age, an information sheet and consent form will be read out loud by the interviewer in a language with which the participants are familiar, and the main aims, format and implications of the study will be explained to participants (Annex 1a for cases and 1b for controls). Participants will be informed regarding their right to withdraw from the study at any time without penalty, and issues concerning confidentiality

and consent will be addressed in accordance with ethical research standards. Case participants will be made aware that participating in the study is in no way linked to the care they will receive from MSF, and that no incentives will be given for participation in the study.

After research staff has read the information sheet and informed consent forms out aloud to participants, questions will be answered and staff will then request caretakers and husbands to sign the consent form, if participants cannot sign, a thumb print will be requested.

Informed Consent forms and Information Sheets will be translated into Hausa and back translated into English for consistency of language. A copy of the information sheet and informed consent form will be provided to each caretaker/parent of a case or control included in the study.

10 Ethical considerations

The MSF ethical review board, the Usman Danfodiyo University Teaching Hospital (UDUTH) Health Research and Ethics Committee in Nigeria and the Ministry of Health of Nigeria Ethics Department will review the study protocol and it will not be implemented unless approval is obtained from all three boards.

10.1 Benefits

A direct benefit to the at-risk population will come from the strengthening of MSF's current programming by providing essential information from which more effective prevention strategies can be developed. Similarly, dissemination of results will help inform other actors, such as the Ministry of Health, MSF Noma Children's Hospital and other organizations involved in Noma care globally by contributing to the body of knowledge around this disease. Direct benefit to the individual participant is limited to the overarching benefit to the population as a whole.

The collaboration between MSF, the Ministry of Health, MSF Noma Children's Hospital and the Usman Danfodiyo University Teaching Hospital will strengthen these relationships, and increase MSF's credibility with these institutions.

The project will provide insight into potential risk factors for Noma which may allow for the development of early intervention programs as well as targeted education training of health care professionals to increase early identification and treatment of Noma.

10.2 Risks

There is the potential for psychological stress to occur by asking participants to answer sensitive questions which (particularly care takers of cases) could make the care taker feel as if they are somehow to blame for the disease. This risk will be mitigated by ensuring well trained staff conducts the interviews and care is taken during instrument design to minimize risk. Interviews will be terminated if the interviewer observes that the respondent is under undue stress. Regular briefings will be held with interviewers throughout the research process to identify issues and provide further training as required. The MSF Psychology team will be available to provide counselling to participants who request or require assistance.

Great care will be taken to mitigate the psychological risks during the formation of the questionnaire and during implementation by using well trained interviewers. Recall bias could be problematic, as Noma patients would be more likely to recall certain risk factors in

comparison to controls. Care will be taken during questionnaire development and interviewing to try to find alternate ways to ask questions and ensure short recall periods are used where possible.

The principle of justice will be upheld by ensuring those who share in the risks of the project share in the post-study benefits. This will be done by ensuring that the villages that the cases and controls come from are added to the list for potential interventions that are planned due to the results of the study. Individuals participating in the project will be treated equitably and fairly.

The operational area of the Noma project within and outside Sokoto operates at a high level of security. In order to mitigate security risks, all interview teams and researchers will be asked to comply with MSF security guidelines. These guidelines might limit the ability to move to villages to collect appropriate information on all cases and controls. The security implications for the implementation of the study cannot be planned beforehand and will require adjustments at various stages to ensure all risks are mitigated.

11 Community Engagement

Since 2015, MSF has been working on Noma in the MSF Noma Children's Hospital, however our activities in north west Nigeria pre date this year substantially, MSF are actively working in nutrition, mother-child care and lead poisoning in Zamfara and Anka. MSF's connection to the community, specifically for Noma, is slowly increasing as the project develops. To date it has focused mostly on active case finding for Noma through established health centres and by spreading messages by radio to inform the population of our existing surgical activities for Noma. MSF's ongoing community engagement strategy is to target health providers in PHCs and nutrition centres and hospitals focusing on prevention, early detection, treatment and referral. Community leaders, traditional healers and community members are met and the MSF projects are discussed. Noma hospital patients, caretakers as well as beneficiaries from other MSF projects and the general population in the catchment area are involved with the dissemination of health promotional material. Surveillance to understand the prevalence of Noma cases in MSF areas of operations in coordination with a surveillance team is conducted. The Ministry of Health supports in various ways to address this neglected disease.

12 Limitations

Noma has a reported 90% mortality rate, meaning that those seeking treatment are not only a small portion of patients who have developed the disease, they are also the portion of the Noma population which had the least severe complications from the disease. Risk factors assessed from this project for this portion of the Noma population could thus not truly represent all the risk factors that affect Noma patients. Further studies would be needed in order to ascertain if the risk factors of those Noma cases which were fatal differ from those which were not. The project is being conducted in a high security risk area, which could potentially make travelling to villages to interview controls impossible, rendering the number of control information gathered less than optimal. Finding matching controls could also be difficult as patients could come from far away. If these issues lead to a need for using controls from the MSF feeding center, then most risk factors around nutrition will need to be carefully re-assessed in terms of their value in the objectives of the study. We will be

comparing basic demographic characteristics between cases and controls to ensure that the two populations are stemming from the same/similar source population. However, it is possible that any risk factors related to nutrition will become watered down in this study design due to the fact that controls are being sourced from an existing malnourished group with associated co-morbidities.

13 Study schedule

We have pre-defined the following time points in the implementation of this study:

Output	Estimate Deadline
Submission to MSF ERB	February 2017
Submission to ERB of UDUTH	February 2017
Pre study qualitative implementation (study research in Sokoto)	February 2017
ERB approval MSF and UDUTH	April 2017
Preparation field study (hiring of staff, training of staff, piloting of questionnaires and logistics for field implementation)	May 2017
Study implementation	June 2017
Analysis of data and report write up	July-August 2017
Dissemination of report to stakeholders	September 2017
Submission of manuscript to peer reviewed journal (if relevant)	December 2017

14 Budget

An estimated budget for the study is included in Annex 6.

15 Research staff

- **Annick Lenglet** (MSF Epidemiology Advisor, MSF) will be the Principle Investigator for the study, and will advise on all of the study activities.
- **Elise Farley** (MSF Field Research Staff) will be responsible for creating the protocol, designing the survey instruments, pre-testing the questionnaires on site making necessary administrative tools, working with the onsite team to coordinate research activities, collating and arranging for data to be uploaded to the database, analyzing data, writing up final research report and the dissemination of findings.
- **Suzan Trienekens** (Field Epidemiologist, MSF Sokoto) will assist in the preparation of the field work and the pilot testing of the questionnaires. Additionally, she will assist the Study Researcher in the implementation of the field component of the study in June 2017.
- **Prof. Nma M. Jiya,** (Department of Pediatrics, Usman Danfodiyo University Teaching Hospital, Sokoto)) will be assisting in obtaining ERB approval. He will be assisting the Study Researcher in the implementation of the field component of the study.
- **Dr. Adeniyi Semiyu Adetunji,** (Noma Children's Hospital and the Ministry of Health) will be assisting the Study Researcher in the implementation of the field component of the study.
- **Dr. Mohana Amirtharajah** (Surgical Advisor, MSF) will assist with advice on surgical aspects of the study, including questions, risk factors, and potential aspects for intervention.
- **Karla Bil** (Health Advisor Nigeria, MSF) will assist with health related aspects of the project, including questionnaire development, risk factor assessment, and logistical advice on control assessments.

- **Dr. Saskia van der Kam** (Nutrition Advisor, MSF) will assist in protocol development, including methodological, nutritional and sociological/anthropological aspects, and in reporting.
- **Geke Huisman** (Medical Coordinator Nigeria, MSF) will assist with onsite introductions, context specific questions, logistics advice, questionnaire appropriateness assessments.
- Beverley Stringer (Qualitative Research Advisor, MSF) will assist with qualitative aspects of the project, including study design, discussion guidelines and analysis.

We have included the résumés of the Primary Investigator and the Study Researcher in Annex 7.

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17 Dissemination

The findings will be written up by the Study Researcher (Elise Farley) into an internal report which will be shared with all collaborators for their input. A PowerPoint presentation and pamphlet will be put together and shared with the staff at the MSF Noma Children's Hospital, study participants and those involved with the research project by either the onsite Epidemiologist or Elise Farley (if resources permit). If relevant, a manuscript will be prepared for submission to a peer-reviewed journal. MSF will use the information to guide programming to prevent Noma and to stop early onset of Noma.

18 Annexes

Annex 1a: Information sheet and consent form for caretakers of cases
Annex 1b: Information sheet and consent form for caretakers of controls
Annex 1c: Information sheet and consent form for Focus Group Discussion participants
Annex 1d: Information sheet and consent form for Key Informant Interview participants
Annex 2: Individual questionnaire Noma case English
Annex 3: Individual questionnaire Noma control English
Annex 4: Key Informant Interview Guide
Annex 5: Focus Group Discussion Guide
Annex 6: Estimated study budget
Annex 7: CVs Annick Lenglet and Elise Farley

19 References

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