

## **Appendix 1: Methods.**

### **Eligibility Criteria.**

The main restriction for inclusion was that incidences of pellagra should have involved people living in South Africa (including areas at some stage considered homelands), and only people living in South Africa. None of the following were considered a reason for exclusion: age, gender, race, language or date of occurrence. The rationale for this is evident as the objective was to document all incidences of pellagra in South Africa – from the first recorded incident of the disease until this manuscript was submitted.

Information was sourced for indications of niacin (B3) deficiency applying the same inclusion/exclusion criteria. The rationale was that niacin deficiency is considered the primary cause of pellagra.

### **Information sources.**

We searched scientific databases including EBSCO Host (Academic Search Complete; Africa-Wide Information; AHFS Consumer Medication Information; eBook Collection (EBSCOhost); E-Journals; Family & Society Studies Worldwide; Health Source: Nursing/Academic Edition; MasterFILE Premier; PsycARTICLES; PsycINFO; Social Work Abstracts; TOC Premier, as well CINAHL Complete; MEDLINE Complete; Dentistry & Oral Sciences Source), Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) as well as Scopus. For information on search strategies and latest dates of coverage see under section "Searches".

In addition to searches on pellagra or niacin deficiency in South Africa, searches were also performed on the South African burden of disease, based on hospital admissions and on causes of death. The rationale was to see whether pellagra ever featured among the top ten or twenty causes of death or reasons for hospital admissions. We furthermore performed a search on pellagra or niacin deficiency specifically against the names of all existing and erstwhile psychiatric institutions in South Africa. The rationale for the latter was that special hospitals were filled in Europe, Egypt and the USA for what was referred to as the pellagrous insane.

The structured databases rarely returned findings from the late 19th, early 20th century from South Africa. We thus manually searched through library and other archives, as well as the

internet. Reference lists from an important 1929 publication by Cluver<sup>(1)</sup> and a 1951 book by Gillman and Gillman<sup>(2)</sup> facilitated manual searches through archives and the internet.

We searched websites, and where necessary, directly requested assistance from reputable organisations such as the South African Medical Research Council; Statistics South Africa; South African Department of Health; South African Data Archive (SADA); the Historical Papers Research Archive, University of the Witwatersrand; Southern Africa Labour & Development Research Unit (SALDRU), University of Cape Town; the Cory Library Collection, Rhodes University; William Cullen Library, University of the Witwatersrand; South African History Online (SAHO); World Health Organization Regional Office for Africa; National Archives and Record Services of South Africa Head Office, as well as Provincial Archive Service, including Eastern Cape Provincial Archives, Free State Provincial Archives, Gauteng Provincial Archives, KwaZulu-Natal Provincial Archives, Pietermaritzburg Archives Repository, Ulundi Archives Repository, Limpopo Provincial Archives Service, Mpumalanga Provincial Archives Service, Northern Cape Provincial Archives Service, North West Provincial Archives and Records Services and Western Cape Provincial Archives and Records Service.

Information from 93 sources on pellagra and niacin deficiency were combined in Table 1.

### **Searches**

Search strategies were developed and executed by the relevant information specialist at the Department of Library Services.

The search for information started in 2018 and structured electronic searches were continued intermittently over the study period. Initial search words included South Africa, pellagra, niacin deficiency and vit3 deficiency, but varied when specific aspects of the study were investigated. Final searches were performed in February 2021.

Examples of search strategies:

#### **1. Scopus search strategy covering the period 1800 to February 2021.**

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(( TITLE-ABS-KEY ( pellagra ) ) OR ( TITLE-ABS-EY ( niacin ) ) ) AND ( ( TITLE-ABS-KEY ( {south africa} ) )
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OR ( AFFILCOUNTRY ( "south africa" ) ) ) AND ( EXCLUDE ( SUBJAREA , "AGRI" ) OR EXCLUDE ( SUBJAREA , "ENVI" ) OR EXCLUDE ( SUBJAREA , "EART" ) OR EXCLUDE ( SUBJAREA , "MATE" ) OR EXCLUDE ( SUBJAREA , "PHYS" ) OR EXCLUDE ( SUBJAREA , "VETE" ) )

## **2. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R). 1946 to February 01, 2021.**

Surprised that in South Africa few associations were found between pellagra and neuropsychiatry, as opposed to the fact that special hospitals existed in Europe, Egypt and the USA for pellagrins with neuropsychiatric disorders, yet another Ovid MEDLINE(R) search was performed in 2021 which included all existing and erstwhile psychiatric institutions in South Africa.

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Search strategy:

- 1 pellagra.mp. or exp \*Pellagra/ (1559)
- 2 niacin.mp. or exp \*Niacin/ (13648)
- 3 deficiency diseases.mp. or exp \*Deficiency Diseases/ (75882)
- 4 (deficiency adj disease\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (11020)
- 5 (vitamin adj deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1363)
- 6 weskoppies.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (34)
- 7 sterckfontein.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept

word, unique identifier, synonyms] (143)

8 (fort adj england).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1)

9 (tower adj hospital).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (193)

10 stikland.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (16)

11 valkenburg.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17)

12 (elizabeth adj donkin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1)

13 komani.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2)

14 (tara adj hospital).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)

15 (oranje adj hospital).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4)

16 (fort adj napier).mp. [mp=title, abstract, original title, name of substance word, subject

heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1)

17 1 or 2 or 3 or 4 or 5 (92379)

18 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (411)

19 17 and 18 (0)

20 (South adj Africa).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (56285)

21 1 or 2 (14885)

22 20 and 21 (5)

### 3. EBSCO Host (various data bases as shown below). No limitations on period.

Search strategy

Search ID#	Search Terms	Search Options	Last Run Via	Results
S7	S4 AND S5 AND S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	11
S6	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA	38,524

			PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	
S5	"south africa"	Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	1,669,951
S4	Psychiatr*	Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health	4,161,763

			Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	
S3	"vitamin b3"	Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	28,319
S2	Pellagra	Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	9,848
S1	niacin	Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA	49,244

		subjects Search modes - Boolean/Phrase	PsycInfo;Academic Search Complete;Africa-Wide Information;AHFS Consumer Medication Information;APA PsycArticles;CINAHL;Dentistry & Oral Sciences Source;eBook Collection (EBSCOhost);Family & Society Studies Worldwide;Health Source - Consumer Edition;Health Source: Nursing/Academic Edition;MEDLINE;Social Work Abstracts;TOC Premier;eBook Academic Collection (EBSCOhost)	
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### **Selection of sources of evidence**

All sources were initially documented in a form comprised of columns for source (reference), date/period of observation/outbreak, area/city/province/hospital/clinic, number of subjects studied, number of subjects studied that were diagnosed with pellagra, mortality data if available, ages/adults/children, gender, race, consumption of maize. This was followed by a) screening for and removal of duplicates, b) screening for uncorroborated statements and figures. Editorials and congress contributions published in refereed journals, without credible citations are noted as such in Table 1.

### **Data charting process.**

As this was a very large study a comprehensive data-charting form, presented as Table 1, was developed in an attempt to somewhat reduce the information overload and to keep a check on the word count of the results section. Information for the table was extracted from the form described above for the selection of evidence. Information on niacin deficiency was similarly tabulated with inclusion of the methods used to estimate the levels of niacin, e.g., nicotinic acid status based on urinary excretion of N<sup>1</sup>-methyl nicotinamide (N<sup>1</sup>-Me) and N<sup>1</sup>-methyl-2-pyridone-5-carboxylamide (2-pyridone). Two reviewers were involved in charting and in verifying the data. They discussed the results and continuously updated the data.

### **Data items**

The main data items were pellagra, niacin and vitamin B3 deficiency. However, data items varied when specific aspects of the study, e.g., fortification of maize, were studied.



### **Critical Appraisal of Individual Sources of Evidence**

The greater part of the sources of evidence was from accredited medical and other scientific journals, and from original archives and archived documentation.

Unreferenced/unsubstantiated figures given in the gray literature for the prevalence of pellagra/niacin deficiency in South Africa, or where incorrect citations were given, were eliminated as sources of information. References provided in gray literature were followed up to ensure that they contained credible information and that they indeed contain the information claimed in the gray source. Unstinting support was received from the information specialist in attempts to find 'untraceable' references.

### **Synthesis of results**

Information extracted and collated from the form described under the section dealing with the data charting process is summarised and presented in Table 1 of the manuscript. Extracted from Table 1, as it is not obvious without time-consuming scrutiny on behalf of the reader, is presented quantitative estimations of reported incidences of pellagra in adults, children, different races, dermatological and neuropsychiatric associations.

### **References**

1. Cluver EH (1929) Pellagra among the maize-eating natives of the Union of South Africa. *Br Med J* 2, 751-754.
2. Gillman J & Gillman T (1951) Perspectives in human malnutrition. A contribution to the biology of disease from a clinical and pathological study of chronic malnutrition and pellagra. *New York: Grune and Stratton* 25-39.