

**S1 Table1: Grouping and background information on inflammatory markers chosen for analysis in cerebrospinal fluid of South African pneumococcal meningitis patients**

| Inflammatory marker* | Group** | Other names           | Known functions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Reference(s) |
|----------------------|---------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| NGF-β                | 2       |                       | Neurotrophic growth factor which has positive effects on axon growth, cell survival and postnatal development                                                                                                                                                                                                                                                                                                                                                                                                                            | [1]          |
| CD40-Ligand          | 4       |                       | Member of the TNF receptor family and essential for antibody response to thymus dependent antigens, Important for the generation of a robust T-cell dependent memory response,                                                                                                                                                                                                                                                                                                                                                           | [2, 3]       |
| ENA-78 (LIX)         | 3       | CXCL5                 | Proposed to play a role in recruitment of neutrophils, promotion of angiogenesis and remodeling of connective tissue, In mice, indication that CXCL5 contributes to resistance of pneumococcal infection,                                                                                                                                                                                                                                                                                                                                | [4]          |
| Eotaxin              | 3       | CCL11                 | Potent and eosinophilic specific chemoattractant, Proposed to play a role in heightened inflammatory response of aged mice when exposed to <i>S. pneumoniae</i> ,                                                                                                                                                                                                                                                                                                                                                                        | [5]          |
| G-CSF                | 2       | CSF-3                 | Involved in the stimulation of proliferation and differentiation of hematopoietic progenitor cells, In a mouse model, proposed to improve spatial learning and to stimulate neurogenesis after pneumococcal meningitis,                                                                                                                                                                                                                                                                                                                  | [6]          |
| GM-CSF               | 1       | CSF-2                 | High levels at sites of inflammation and autoimmunity, Cytolytic activity of a pneumococcal D39 strain was found to induce increased expression of genes encoding GM-CSF,                                                                                                                                                                                                                                                                                                                                                                | [7-9]        |
| Gro-α                | 3       | KC<br>CXCL1<br>MGSA-α | In a sequencing study to determine the role of genetic variation on pneumococcal meningitis susceptibility and outcome, a Gro-α gene had a strong signal for susceptibility, Suggested to be a major chemoattractant of leukocytes into the subarachnoid space during meningitis,                                                                                                                                                                                                                                                        | [10, 11]     |
| HGF                  | 2       | -                     | Shown to regulate acute and chronic inflammation in different disease models, and found to be elevated in CSF of patients with acute bacteria/probable bacterial meningitis compared to nonbacterial CNS infections,                                                                                                                                                                                                                                                                                                                     | [12-14]      |
| IFN-α                | 1       | -                     | Mainly involved in innate immunity and secreted by immune and non-immune cells in answer to viral infections,                                                                                                                                                                                                                                                                                                                                                                                                                            | [15]         |
| IFN-γ                | 1       | -                     | Primarily secreted by activated T-cells and natural killer cells, Can promote macrophage activation, mediate antiviral and antibacterial immunity, enhance antigen presentation, orchestrate activation of innate immune system, coordinate lymphocyte-endothelium interaction, regulate Th1/Th2 balance and control cellular proliferation and apoptosis, Observations indicate that there is an association between IFN-γ driven acute brain pathology and the long-term neurological sequelae resulting from pneumococcal meningitis, | [16, 17]     |
| IL-10                | 1       | -                     | Cytokine with anti-inflammatory properties and may play an important role in preventing damage to the host by limiting the immune response towards pathogens, Proposed to modulate the magnitude of the neutrophil influx, Higher concentrations in severe sepsis patients compared to sepsis patients has been shown,                                                                                                                                                                                                                   | [5, 18, 19]  |
| IL-12p40             | 1       | -                     | The p40 subunit is distantly related to the IL-6 receptor, Upregulation via binding of IFN-γ (produced upon TLR activation),                                                                                                                                                                                                                                                                                                                                                                                                             | [20]         |
| IL-13                | 1       | -                     | Involved in allergic inflammation, mainly involved in parasitic infections,                                                                                                                                                                                                                                                                                                                                                                                                                                                              | [21, 22]     |
| IL-15                | 1       | -                     | Pleiotropic cytokine which has functions including regulating tissue repair, modulating inflammation and activating natural killer cells, upon infections with bacteria, IL-15 expression increases,                                                                                                                                                                                                                                                                                                                                     | [23, 24]     |
| IL-17A               | 1       | CTLA-8                | Plays a protective role in host defense against certain pathogens at the epithelial and mucosal barriers, A deficiency in IL-17A/F has been related to a high susceptibility to <i>Streptococcus pneumoniae</i> and other infections in humans, A dysregulation of IL-17A/F production can result in pro-inflammatory cytokine expression and chronic inflammation, IL-17 has been shown to be elevated in CSF of children with bacterial meningitis and is proposed to play a key role in neutrophil infiltration into the CSF,         | [25-27]      |
| IL-17F               | 1       | -                     | A deficiency in IL-17A/F has been related to a high susceptibility to <i>Streptococcus pneumoniae</i> and other infections in humans, A                                                                                                                                                                                                                                                                                                                                                                                                  | [26]         |

| Inflammatory marker* | Group** | Other names           | Known functions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Reference(s)        |
|----------------------|---------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
|                      |         |                       | dysregulation of IL-17A/F production can result in pro-inflammatory cytokine expression and chronic inflammation,                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                     |
| IL-1 $\alpha$        | 1       | -                     | IL-1 $\alpha$ is a dual function cytokine which binds both to DNA and to its cell membrane receptor, In the nucleus, it serves to increase gene expression of IL-8 for example,<br>Has been shown to play a role in BBB disruption,                                                                                                                                                                                                                                                                                                                                                           | [28-30]             |
| IL-1 $\beta$         | 1       | -                     | Induced by microbial products via the TLR ligands, shown to be increased within a short time after exposure of immune cells to LPS: Higher concentrations in severe sepsis compared to sepsis patients has been shown, It has been described as a marker of inflammatory activity in the CSF and is related to clinical outcome parameters in bacterial meningitis,<br>In a murine model of pneumococcal meningitis, the upregulation in was independent of CSF leukocytosis, pneumococcal pneumolysin and H <sub>2</sub> O <sub>2</sub> but was induced by pneumococcal cell wall fragments, | [18, 28, 31-34]     |
| IL-2                 | 1       | -                     | Plays a role in regulation of immune activation and homeostasis, HIV infection has been shown to lead to a deficiency in IL-2 production, IN a comparison study of cytokines in CSF between pneumococcal and meningococcal meningitis, IL-2 concentrations were higher in pneumococcal meningitis,                                                                                                                                                                                                                                                                                            | [35, 36]            |
| IL-4                 | 1       | -                     | Proposed to play a role during late stages of pneumococcal meningitis, Additionally, to playing a role in immunity, evidence points to a role in memory and learning in the normal brain,                                                                                                                                                                                                                                                                                                                                                                                                     | [37, 38]            |
| IL-5                 | 1       | -                     | Plays a role in hematopoiesis and largely plays a role in allergic or eosinophilic inflammatory diseases,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | [9]                 |
| IL-6                 | 1       | -                     | Pro-inflammatory cytokine, has been shown useful as a factor for diagnostic, clinical severity and prognosis, Higher concentrations in severe sepsis compared to sepsis patients, and in patients with fatal outcome has been shown as well as a strong negative relationship of conc, with neurological sequelae of concentration in plasma,<br>Is a well-studied cytokine in animal models of bacterial meningitis,                                                                                                                                                                         | [18, 30, 36, 39-42] |
| IL-7                 | 1       | -                     | Important for T-cell development and survival as well as homeostasis of mature T-cells, proposed to play an essential role in the anti-polysaccharide response towards <i>streptococcus pneumoniae</i> ,                                                                                                                                                                                                                                                                                                                                                                                      | [43-45]             |
| IL-8                 | 3       | CXCL8                 | Important chemoattractant for neutrophils, Higher concentrations in severe sepsis compared to sepsis patients has been shown, IL-8 differences in concentration between serotypes in a rabbit model of pneumococcal meningitis, Pneumolysin has been found to be a major factor influencing the IL-8 response from human nasopharyngeal epithelial,                                                                                                                                                                                                                                           | [11, 18, 46-48]     |
| IP-10                | 3       | CXCL10                | Reported to be enhanced in patients co-infected with <i>Streptococcus pneumoniae</i> and Influenza and suggested to be a biomarker capable of severity prediction various diseases,                                                                                                                                                                                                                                                                                                                                                                                                           | [38, 49, 50]        |
| LIF                  | 1       | -                     | Member of the interleukin-6 cytokine family which all activate the signal transducer and activator of transcription 3 (STAT3), STAT3 influences stem and progenitor cells,                                                                                                                                                                                                                                                                                                                                                                                                                    | [51]                |
| MCP-1                | 3       | CCL2<br>MCAF<br>TDCF  | Plays a role in BBB disruption through recruitment of monocytes/macrophages, MCP-1 plasma levels have been suggested to be associated with sepsis induced organ dysfunction,                                                                                                                                                                                                                                                                                                                                                                                                                  | [52-54]             |
| MCP-3                | 3       | CCL7                  | MCP-3 is a chemokine which attracts Macrophages which may play a role in chronic inflammation,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | [55, 56]            |
| M-CSF                | 2       | CSF-1                 | Known to regulate tissue macrophage homeostasis, Evidence is emerging that, in mice, the M-CSF signaling could directly control the development and maintenance of microglia cells,                                                                                                                                                                                                                                                                                                                                                                                                           | [57]                |
| MIG                  | 3       | CXCL9                 | Is involved in the regulation of leukocyte trafficking and is induced by IFN- $\gamma$ , It has been shown to induce antibacterial activity <i>in vitro</i> ,                                                                                                                                                                                                                                                                                                                                                                                                                                 | [58]                |
| MIP-1 $\alpha$       | 3       | CCL3<br>LD78 $\alpha$ | Has been suggested to be beneficial in <i>Streptococcus pneumoniae</i> induced meningitis, Increase of MIP-1 $\alpha$ was demonstrated in meningitis <i>in vivo</i> and in glial cells <i>in vitro</i> in reaction to <i>Streptococcus pneumoniae</i> ,                                                                                                                                                                                                                                                                                                                                       | [59, 60]            |
| MIP-1 $\beta$        | 3       | CCL4                  | Has both inflammatory and chemokinetic properties and binds to the CCR5 receptor, it is one of the major HIV suppressive factors produced by CD8+ T-cells, It is a major chemoattractant for natural killer cells,                                                                                                                                                                                                                                                                                                                                                                            | [60-62]             |
| PAI-1                | 4       | Serpin                | PAI-1 is a serine protease inhibitor (modulation of serine protease activities is essential for coagulation), Serpins are present in both host and pathogen, Host serpins may directly inhibit pathogen proteases and pathogen binding, One study mentioned a positive correlation between PAI-1 concentration in CSF and the BBB breakdown,                                                                                                                                                                                                                                                  | [63-65]             |

| Inflammatory marker*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Group** | Other names | Known functions                                                                                                                                                                                                                                                                                                                       | Reference(s)    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| PDGF-BB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2       | -           | PDGF's play an important role in angiogenesis and have been introduced in clinics as a wound healing therapy,                                                                                                                                                                                                                         | [66]            |
| Resistin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4       | ADSF        | Resistin was originally known as an adipocyte specific hormone and is thought to be a link between obesity, insulin resistance and diabetes, there has been a report of astrocytes expressing resistin, High levels tend to be associated with a pro-inflammatory effect and have been shown to stimulate pro-inflammatory cytokines, | [67, 68]        |
| SCF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4       | -           | SCF is important for the maturation and infiltration of mast cells,                                                                                                                                                                                                                                                                   | [69]            |
| sFas-Ligand                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 4       | -           | The Fas-Ligand is a member of the TNF-superfamily, the primary function is the induction of apoptosis, It is a well-known marker of apoptosis, In patients with bacteremia, it has been associated with high sequential organ failure assessment scores,                                                                              | [70] [48]       |
| TGF- $\alpha$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 2       | -           | TGF- $\alpha$ from astrocytes has been reported to play a neuroprotective role against neurotoxic insults and has been shown to be upregulated during brain injury,                                                                                                                                                                   | [71-75]         |
| TNF- $\alpha$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1       | -           | Up-regulation in neurons and astrocytes in the hippocampus during pneumococcal meningitis in murine models has been noted and is a marker of inflammatory activity in the CSF, It has also been noted as a parameter correlating to the clinical outcome in bacterial meningitis,                                                     | [18, 34, 76-78] |
| TRAIL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 4       | -           | A member of the TNF-superfamily, it is expressed by various immune cells and is a well-known marker of apoptosis, in an experimental model of <i>Streptococcus pneumoniae</i> caused meningitis, TRAIL-/- mice showed prolonged inflammation, augmented clinical impairment and increased hippocampal apoptosis                       | [79, 80]        |
| VEGF-A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2       | -           | Stimulates angiogenesis, vascular repair and regeneration and may also promote neuronal functions such as neurogenesis, neuronal migration neuronal survival and axon guidance,                                                                                                                                                       | [81]            |
| <p><b>*Abbreviations:</b> Epithelial-derived neutrophil-activation protein (ENA), Granulocyte (G), Colony stimulating factor (CSF), Macrophage (M), Growth related oncogene (Gro), Hepatocyte growth factor (HGF), Interferon (IFN), Interleukin (IL), Interferon (IFN), induced protein (IP), IL-6 family cytokine (LIF), Monocyte chemotactic protein (MCP), Monokine induced by IFN-<math>\gamma</math> (MIG), Macrophage inflammatory protein (MIP), Plasminogen activator inhibitor (PAI), Platelet derived growth factor (PDGF), Stem cell factor (SCF), Tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), Vascular endothelial growth factor (VEGF), Neurotrophic growth factor (NGF), Transforming growth factor (TGF)</p> <p><b>**Group 1:</b> cytokines, Group 2: growth factors, Group 3: chemokines, Group 4: other inflammatory markers [82]</p> |         |             |                                                                                                                                                                                                                                                                                                                                       |                 |

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**S2 Table:** Demographic and clinical characteristics of patients with meningitis included in the analysis

| Variable            |               | n/N   | %    |
|---------------------|---------------|-------|------|
| PROVINCE            | Eastern Cape  | 11/57 | 19.3 |
|                     | Free State    | 8/57  | 14.0 |
|                     | Gauteng       | 13/57 | 22.8 |
|                     | KwaZulu-Natal | 3/57  | 5.3  |
|                     | Mpumalanga    | 9/57  | 15.8 |
|                     | North West    | 2/57  | 3.5  |
|                     | Western Cape  | 7/57  | 12.3 |
|                     | Missing       | 4/57  | 7.0  |
| GENDER              | Female        | 24/57 | 42.1 |
|                     | Male          | 28/57 | 49.1 |
|                     | Missing       | 5/57  | 8.8  |
| HIV                 | Negative      | 9/57  | 15.8 |
|                     | Positive      | 34/57 | 59.7 |
|                     | Missing       | 14/57 | 24.6 |
| AGE CATEGORY        | <1y           | 8/57  | 14.0 |
|                     | 1-4y          | 2/57  | 3.5  |
|                     | 5-14y         | 4/57  | 7.0  |
|                     | 15-24y        | 1/57  | 1.8  |
|                     | 25-44y        | 25/57 | 43.9 |
|                     | 45-64y        | 10/57 | 17.5 |
|                     | >=65y         | 2/57  | 3.5  |
|                     | Missing       | 5/57  | 8.8  |
| RACE                | Other         | 10/57 | 17.5 |
|                     | Black         | 36/57 | 63.2 |
|                     | Missing       | 11/57 | 19.3 |
| SEROTYPE            | 14            | 2/57  | 3.5  |
|                     | 19F           | 2/57  | 3.5  |
|                     | 3             | 5/57  | 8.8  |
|                     | 6A            | 1/57  | 1.8  |
|                     | 7F            | 1/57  | 1.8  |
|                     | 19A           | 2/57  | 3.5  |
|                     | 8             | 7/57  | 12.3 |
|                     | 9N            | 2/57  | 3.5  |
|                     | 10A           | 2/57  | 3.5  |
|                     | 12F           | 5/57  | 8.8  |
|                     | 15B/C         | 3/57  | 5.3  |
|                     | 22F           | 2/57  | 3.5  |
|                     | 16F           | 1/57  | 1.8  |
|                     | 23A           | 2/57  | 3.5  |
|                     | 31            | 1/57  | 1.8  |
|                     | 18A           | 1/57  | 1.8  |
|                     | 6D            | 1/57  | 1.8  |
|                     | 22A           | 1/57  | 1.8  |
|                     | Undefined*    | 16/57 | 28.1 |
| IN-HOSPITAL OUTCOME | Recovered     | 31/57 | 54.4 |



| Variable                       |         | n/N   | %    |
|--------------------------------|---------|-------|------|
|                                | Died    | 17/57 | 29.8 |
|                                | Missing | 9/57  | 15.8 |
| UNDERLYING MEDICAL CONDITION** | No      | 32/57 | 56.1 |
|                                | Yes     | 11/57 | 19.3 |
|                                | Missing | 14/57 | 24.6 |

\***Undefined serotypes** include pool G serotypes, non-typables and serotypes not distinguishable by polymerase chain reaction

\*\***Underlying medical condition** includes pre-disposing conditions defined as any one or more of the following: burns, chronic lung disease (including asthma, chronic obstructive pulmonary disorder, cystic fibrosis), chronic liver disease, chronic renal disease, cardiac conditions (including valvular disease and heart failure), cerebrovascular accident, stroke, neuromuscular diseases, cerebral palsy, metabolic diseases (including diabetes mellitus), head injury, surgery, cerebrospinal fluid leaks, ventricular shunts, cochlear implants, primary immunodeficiency conditions, complement deficiency, immunosuppression treatment (steroids/chemo/cancer treatment) protein-energy malnutrition, functional or anatomic asplenia (including sickle cell disease), malignancy, organ transplant, chromosomal conditions (including down syndrome), prematurity and aplastic anaemia,

**S3 Table:** Cytokine concentration (pg/ml) of residual cerebrospinal fluid collected from South African meningitis patients (2018 – 2019) according to diagnosed serotype

| Serotype*   |             |              |            |             |             |              |            |             |              |              |                |              |              |              |             |              |              |             |                      |
|-------------|-------------|--------------|------------|-------------|-------------|--------------|------------|-------------|--------------|--------------|----------------|--------------|--------------|--------------|-------------|--------------|--------------|-------------|----------------------|
| Marker**    | 14<br>n = 2 | 19F<br>n = 2 | 3<br>n = 5 | 6A<br>n = 1 | 7F<br>n = 1 | 19A<br>n = 2 | 8<br>n = 7 | 9N<br>n = 2 | 10A<br>n = 2 | 12F<br>n = 5 | 15B/C<br>n = 3 | 22F<br>n = 2 | 16F<br>n = 1 | 23A<br>n = 2 | 31<br>n = 1 | 22A<br>n = 1 | 18A<br>n = 1 | 6D<br>n = 1 | Undefined***<br>n=16 |
| CD40        | 17.51       | 62.30        | 11.72      | 16.45       | 1.01        | 15.21        | 26.74      | 14.07       | 22.22        | 16.61        | 25.83          | 18.22        | 14.55        | 2.95         | 70.64       | 29.65        | 13.53        | 1.01        | 15.90                |
| ENA         | 89.46       | 180.33       | 43.53      | 34.37       | 0.00        | 194.13       | 1777.73    | 111.62      | 513.09       | 2875.83      | 4482.06        | 1134.80      | 38.21        | 321.93       | 228.54      | 14890.95     | 12.50        | 0.00        | 1068.85              |
| Eotaxin     | 7.59        | 6.97         | 5.52       | 12.62       | 3.68        | 6.45         | 5.96       | 4.03        | 6.28         | 4.67         | 7.43           | 5.14         | 3.80         | 2.15         | 22.19       | 8.59         | 4.21         | 2.52        | 4.51                 |
| G-CSF/CSF-3 | 909.24      | 307.49       | 302.52     | 46.98       | 0.00        | 220.67       | 2335.61    | 1936.42     | 7308.39      | 1967.74      | 1353.57        | 309.90       | 0.00         | 0.00         | 1576.50     | 14057.75     | 63.61        | 0.00        | 1323.91              |
| GM-CSF      | 81.30       | 124.59       | 95.09      | 242.21      | 0.00        | 16.86        | 53.52      | 31.33       | 135.53       | 45.42        | 0.00           | 0.00         | 0.00         | 0.00         | 719.56      | 0.00         | 0.00         | 0.00        | 8.65                 |
| Gro-α/KC    | 1213.69     | 207.17       | 122.94     | 618.29      | 13.11       | 673.53       | 626.84     | 35.91       | 704.02       | 611.79       | 610.24         | 816.47       | 320.54       | 283.93       | 1146.57     | 2153.01      | 51.81        | 0.00        | 355.11               |
| HGF         | 7419.35     | 4950.27      | 7449.37    | 9138.10     | 25494.03    | 17889.07     | 11119.48   | 9868.78     | 5954.55      | 9812.87      | 200030.70      | 20399.02     | 7630.99      | 7137.01      | 1676.77     | 282928.90    | 15617.22     | 38.60       | 7300.61              |
| IFNα        | 1.85        | 2.36         | 1.62       | 1.97        | 2.47        | 1.65         | 2.08       | 1.36        | 2.72         | 1.42         | 1.39           | 1.73         | 0.76         | 0.22         | 9.63        | 1.43         | 3.30         | 0.00        | 0.92                 |
| IFNγ        | 256.25      | 37.62        | 758.25     | 443.71      | 6079.63     | 5718.53      | 66.06      | 127.89      | 140.26       | 209.97       | 3258.66        | 246.15       | 23.57        | 7.82         | 151.28      | 304.63       | 696.84       | 0.00        | 302.49               |
| IL-10       | 637.30      | 159.34       | 947.48     | 2745.65     | 56.16       | 914.08       | 1718.05    | 2959.07     | 673.73       | 2971.62      | 868.56         | 3127.14      | 1699.70      | 72.04        | 383.49      | 2065.47      | 5614.52      | 0.00        | 617.06               |
| IL-12p40    | 128.21      | 8.03         | 45.33      | 43.07       | 59.31       | 15.28        | 70.69      | 22.02       | 36.36        | 137.33       | 36.05          | 38.25        | 28.29        | 19.64        | 11.09       | 7.29         | 123.82       | 1.28        | 38.76                |
| IL-13       | 3.19        | 1.85         | 5.28       | 7.42        | 1.30        | 6.07         | 5.35       | 1.65        | 6.01         | 3.45         | 1.67           | 4.97         | 0.00         | 0.89         | 19.74       | 2.96         | 0.00         | 7.53        | 2.34                 |
| IL-15       | 26.19       | 39.63        | 23.86      | 18.78       | 28.42       | 21.92        | 35.24      | 13.92       | 44.93        | 16.39        | 23.70          | 24.25        | 15.46        | 11.71        | 118.23      | 40.01        | 9.14         | 16.16       | 18.53                |
| IL-17A      | 46.34       | 109.06       | 438.26     | 30.06       | 32.96       | 277.02       | 109.73     | 24.97       | 120.22       | 33.95        | 11.69          | 13.80        | 15.99        | 2.87         | 158.69      | 499.52       | 29.81        | 0.46        | 73.05                |
| IL-1α       | 63.18       | 21.51        | 30.50      | 34.16       | 64.88       | 38.58        | 81.44      | 25.27       | 42.62        | 93.08        | 57.02          | 36.56        | 18.35        | 31.36        | 39.09       | 38.14        | 197.82       | 0.24        | 87.42                |
| IL-1β       | 2410.06     | 185.55       | 1385.04    | 1479.06     | 522.10      | 1281.66      | 3628.90    | 2624.89     | 2239.10      | 4239.05      | 895.56         | 741.61       | 415.00       | 372.62       | 540.10      | 731.82       | 4459.04      | 0.07        | 1933.67              |
| IL-2        | 69.45       | 48.03        | 34.68      | 58.02       | 2.91        | 25.48        | 29.13      | 21.57       | 53.10        | 28.92        | 13.27          | 6.91         | 9.40         | 1.81         | 203.88      | 17.24        | 20.39        | 0.00        | 17.31                |
| IL-4        | 43.19       | 38.12        | 27.54      | 28.51       | 12.74       | 36.06        | 38.89      | 22.57       | 58.68        | 32.75        | 24.36          | 18.02        | 19.67        | 11.22        | 144.84      | 42.26        | 15.26        | 0.00        | 19.19                |
| IL-5        | 25.10       | 12.41        | 0.00       | 65.43       | 24.85       | 16.81        | 28.72      | 12.30       | 3.94         | 9.53         | 4.10           | 0.00         | 0.00         | 40.32        | 12.30       | 0.00         | 13.43        | 0.00        | 7.68                 |
| IL-6        | 7523.75     | 14133.38     | 7887.79    | 3247.48     | 6455.15     | 10615.81     | 8957.10    | 10498.69    | 13779.67     | 9342.78      | 7600.77        | 6337.28      | 4019.86      | 1601.81      | 16592.72    | 9996.30      | 8535.20      | 0.00        | 6820.39              |
| IL-7        | 6.33        | 12.74        | 9.23       | 7.99        | 0.10        | 10.39        | 5.73       | 1.49        | 12.20        | 2.51         | 3.14           | 1.18         | 0.72         | 0.00         | 70.32       | 3.93         | 0.57         | 0.42        | 2.89                 |
| IL-8        | 10452.04    | 11543.47     | 18060.53   | 2971.11     | 32400.29    | 27471.77     | 15753.68   | 23461.58    | 6845.97      | 24200.88     | 22175.01       | 19028.41     | 2893.99      | 26910.03     | 17387.48    | 40459.70     | 20289.43     | 0.00        | 10465.79             |
| IP-10       | 1433.52     | 1141.39      | 292.63     | 113.55      | 471.30      | 3176.56      | 1895.22    | 126.81      | 2153.84      | 1120.59      | 1457.60        | 1597.39      | 49.20        | 1526.00      | 2377.08     | 3641.95      | 125.47       | 0.00        | 1098.30              |
| LIF         | 972.63      | 803.89       | 1309.27    | 680.85      | 1855.50     | 1963.51      | 1577.95    | 1983.48     | 1265.19      | 1671.34      | 2051.83        | 1339.86      | 638.36       | 1682.57      | 1165.22     | 2139.84      | 2514.00      | 0.00        | 1267.19              |
| M-CSF       | 507.08      | 57.42        | 1453.00    | 717.94      | 1053.10     | 1274.42      | 991.29     | 1349.47     | 273.80       | 905.74       | 1588.13        | 1472.53      | 531.76       | 343.13       | 210.29      | 410.57       | 1865.73      | 0.00        | 503.59               |
| MCP-1       | 97696.90    | 2977.03      | 7438.13    | 4377.07     | 193532.80   | 193532.80    | 88489.87   | 26759.60    | 4520.24      | 72099.27     | 8956.57        | 97619.28     | 8701.55      | 99204.34     | 7587.86     | 193532.80    | 8357.30      | 18.73       | 27198.27             |
| MCP-3       | 120.71      | 221.00       | 64.28      | 84.60       | 250.20      | 184.27       | 265.54     | 62.78       | 359.68       | 66.21        | 382.34         | 302.56       | 82.62        | 17.48        | 37.20       | 564.52       | 62.65        | 41.61       | 155.53               |
| MIG         | 1270.56     | 785.93       | 892.28     | 1540.30     | 4886.99     | 2610.45      | 863.34     | 1108.90     | 710.87       | 1270.46      | 3165.75        | 2510.67      | 226.64       | 2054.78      | 280.58      | 3000.25      | 3073.44      | 0.00        | 979.06               |
| MIP1α       | 1390.05     | 386.65       | 470.50     | 636.37      | 37805.91    | 1424.68      | 1225.09    | 799.70      | 754.55       | 703.40       | 709.40         | 2070.82      | 302.85       | 19403.85     | 1687.24     | 746.36       | 1243.44      | 0.00        | 597.41               |
| MIP-1β      | 4511627.00  | 3069.22      | 3008634.00 | 5462.89     | 9024200.00  | 88879.97     | 882864.30  | 15255.90    | 4284.27      | 488985.10    | 15239.24       | 711033.10    | 6063.62      | 9024200.00   | 12227.99    | 69539.58     | 9024200.00   | 0.00        | 593139.70            |
| PAI-1       | 15062.43    | 18875.71     | 19278.55   | 16235.39    | 29995.02    | 32633.63     | 23295.22   | 27402.62    | 28659.42     | 18813.65     | 93134.44       | 40163.86     | 17755.00     | 4439.60      | 14506.07    | 241860.00    | 25421.54     | 0.00        | 16527.27             |
| PDGF-BB     | 19.89       | 94.93        | 73.85      | 40.95       | 0.00        | 91.63        | 36.60      | 0.00        | 99.85        | 8.17         | 75.56          | 0.00         | 0.00         | 0.00         | 560.58      | 76.58        | 0.00         | 56.45       | 17.01                |
| Resistin    | 21975.63    | 29249.79     | 21728.63   | 4204.02     | 20857.36    | 43816.86     | 30576.92   | 43816.86    | 43816.86     | 27086.53     | 25989.33       | 14795.84     | 4757.23      | 11614.90     | 9725.65     | 16330.26     | 10895.39     | 0.00        | 17210.88             |
| SCF         | 3.86        | 11.31        | 2.06       | 13.65       | 1.22        | 3.14         | 16.12      | 1.97        | 8.75         | 3.15         | 1.96           | 2.33         | 1.09         | 0.00         | 10.08       | 21.22        | 1.68         | 0.49        | 6.35                 |
| TNF-α       | 3757.15     | 53.03        | 707.99     | 3473.62     | 200.88      | 1953.84      | 1402.38    | 288.35      | 98.76        | 1093.40      | 1301.85        | 221.06       | 196.58       | 67.88        | 882.82      | 133.28       | 33097.01     | 8.65        | 653.24               |
| TRAIL       | 35.55       | 34.80        | 40.99      | 35.90       | 100.52      | 48.86        | 39.16      | 23.97       | 45.43        | 44.89        | 86.44          | 71.91        | 15.26        | 74.03        | 35.30       | 153.81       | 104.58       | 0.00        | 28.04                |
| VEGF-A      | 2702.28     | 1314.72      | 822.80     | 4521.62     | 8988.32     | 8961.75      | 1929.13    | 843.39      | 329.18       | 2977.90      | 7460.57        | 1526.67      | 396.48       | 14898.85     | 667.67      | 408.27       | 1535.36      | 0.15        | 2368.60              |
| bNGF        | 13.91       | 8.61         | 9.04       | 40.03       | 31.80       | 24.97        | 20.19      | 13.41       | 10.21        | 19.54        | 66.07          | 60.50        | 19.12        | 3.45         | 22.23       | 48.55        | 34.29        | 50.51       | 10.70                |
| sFas Ligand | 26.99       | 1.29         | 6.23       | 17.03       | 38.70       | 52.13        | 57.52      | 11.90       | 20.87        | 18.55        | 23.03          | 26.53        | 2.98         | 0.00         | 45.44       | 129.33       | 14.73        | 0.00        | 11.46                |
| IL-17F      | 0.42        | 0.76         | 6.12       | 0.00        | 21.23       | 46.66        | 1.56       | 5.76        | 0.52         | 2.26         | 1.15           | 0.00         | 0.77         | 0.80         | 0.00        | 32.64        | N/A          | N/A         | 1.11                 |
| TGF-α       | 379.87      | 49.49        | 239.96     | 379.38      | 129.37      | 440.84       | 312.01     | 865.09      | 144.24       | 392.46       | 251.20         | 181.15       | 341.43       | 427.19       | 77.60       | 426.83       | N/A          | N/A         | 247.21               |

\* **Serotype:** listed are the values in pg/ml measured in the CSF of patients for which serotyping was possible. If more than one patient had the same serotype then the average of concentration is listed. Of a total of 57 samples, 16 samples where not possible to serotype or were not possible to distinguish, **\*\*Marker analysis:** We measured the concentrations of inflammatory markers in CSF using a magnetic bead-based 39-plex and 5-plex immunoassay (Human Custom ProcartaPlex 39-plex cat. number PPX-39-MX9HJM4 and 5-plex cat. number PPX-05-MXNKR67, Thermo Fisher Scientific, Waltham, MA, USA). The 39-plex immunoassay included the following markers: CD40-Ligand, Epithelial-derived neutrophil-activation protein (ENA)-78 (LIX), Eotaxin, Granulocyte-Colony stimulating factor (G-CSF)/CSF-3, Granulocyte-Macrophage(GM)-CSF, Growth related oncogene (Gro)-α/KC, Hepatocyte growth factor (HGF), Interferon (IFN)-α, IFN-γ, IL-10, IL-12p40, IL-13, IL-15, IL-17A, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IFN-γ induced protein (IP)-10, IL-6 family cytokine (LIF), M-CSF, Monocyte chemotactic protein (MCP)-1, MCP-3, monokine induced by IFN-γ (MIG), Macrophage inflammatory protein (MIP)-1α, MIP-1β, Plasminogen activator inhibitor (PAI)-1, Platelet derived growth factor (PDGF)-BB, Resistin, Stem cell factor (SCF), TNF-α, TNF-related apoptosis-inducing ligand (TRAIL), Vascular endothelial growth factor (VEGF)-A, Neurotrophic growth factor (bNGF) and sFas-Ligand. The 5-plex immunoassay included the following markers: IFN-γ, IL-17F, IL-6, Transforming growth factor (TGF)-α, TNF-α. The markers were chosen based on a previous publication which measured immune molecules in human CSF (Hornig, Gottschalk et al. 2016) and publications with data on their function and/or concentrations in inflammation, meningitis and/or CSF. **\*\*\*undefined:** includes pool G serotypes (29, 34, 35, 42 and 47), non-typables and serotypes not distinguishable by polymerase chain reaction; for two of the samples, it was not possible to determine IL17F and TGF-α values due to limited amount of available CSF, thus for these two markers the sample number is n = 14. **N/A:** IL-17F and TGF-α determination was not possible due to limited amount of sample volume.

**S4 Table** Associations of serotypes with IL-6 concentrations

| Serotype     | Univariate       |                  |                  | Adjusted*        |                  |                  |
|--------------|------------------|------------------|------------------|------------------|------------------|------------------|
|              | coefficient      | HDI-L**          | HDI-H**          | coefficient      | HDI-L**          | HDI-H**          |
| 10A          | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> |
| 12F          | -3311.72         | -9540.95         | 3120.97          | -1035.2          | -8014.23         | 5717.68          |
| 14           | -6283.22         | -13419.21        | 1377.97          | -4275.64         | -12404.71        | 3594.25          |
| 15B/C        | -6083.59         | -12864.02        | 1012.27          | -4930.73         | -12371.63        | 2364.44          |
| 16F          | -9745.65         | -18727.47        | -165.06          | -8504.7          | -18417.47        | 988.88           |
| 18A          | -5291.19         | -14535.82        | 3903             | -4092.33         | -13777.23        | 5267.04          |
| 19A          | -4060.78         | -11256.57        | 3569.2           | -2804.94         | -11013.53        | 4888.83          |
| 19F          | 397.12           | -7051.84         | 8127.94          | 2978.48          | -5291.28         | 11189.58         |
| 22A          | -3659.03         | -12848.41        | 6062.43          | 218.57           | -10668.68        | 11353.3          |
| 22F          | -7315.9          | -14782.88        | 466.1            | -6303.8          | -14123.68        | 1644.33          |
| 23A          | -12080.67        | -19297.77        | -4390.36         | -10979.91        | -19201.69        | -2869.32         |
| 3            | -6662.45         | -12825.1         | -120.9           | -4791.38         | -11942.64        | 1873.42          |
| 31           | 2739.84          | -6518.99         | 11878.5          | 6866.76          | -4106.6          | 17774.4          |
| 6A           | -10482.07        | -19853.7         | -883.65          | -9096.28         | -18786.04        | 632.44           |
| 6D           | -13650.48        | -22880.48        | -4407.92         | -12712.82        | -22977.67        | -2514.49         |
| 7F           | -7116.51         | -16354.66        | 2000.97          | -7460.98         | -17258.2         | 1992.42          |
| 8            | -2248.77         | -8118.93         | 3897.07          | -168.09          | -6724.55         | 6152.8           |
| 9N           | -5683.89         | -13244.85        | 2131.55          | -3756.32         | -11898.71        | 4453.8           |
| Undefined*** | -6989.64         | -12318.61        | -1058.77         | -5348.64         | -11594.53        | 568.58           |

\***Adjusted coefficient:** adjusted for human immunodeficiency virus (HIV) status and age group

\*\***HDI:** Highest Density Interval of posterior distributions with "-L" = lower bound and "-H" = upper bound

\*\*\***Undefined serotypes** include pool G serotypes (29, 34, 35, 42 and 47), non-typables and serotypes not distinguishable by polymerase chain reaction

**S5 Table** Associations of serotypes with IL-8 concentrations

| Serotype     | Univariate       |                  |                  | Adjusted*        |                  |                  |
|--------------|------------------|------------------|------------------|------------------|------------------|------------------|
|              | coefficient      | HDI-L**          | HDI-H**          | coefficient      | HDI-L**          | HDI-H**          |
| 10A          | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> |
| 12F          | 16558.09         | 1939.89          | 30699.32         | 18361.19         | 2769.29          | 33223.73         |
| 14           | 2939.32          | -14716.4         | 20849.48         | 6256.32          | -11855           | 24113.37         |
| 15B/C        | 14656.28         | -1334.57         | 30098.83         | 17050.5          | 614.6            | 33345.73         |
| 16F          | -4810.28         | -25911.5         | 16297.2          | -2016.15         | -23645.5         | 19078.65         |
| 18A          | 12641.69         | -8343.97         | 33918.62         | 15097.41         | -6887.35         | 37211.63         |
| 19A          | 7625.42          | -10613.2         | 24321.47         | 5022.63          | -13269.9         | 22839.28         |
| 19F          | 3928.54          | -13214.9         | 21050.33         | 1768.36          | -16920.5         | 20464.41         |
| 22A          | 32926.77         | 11196.61         | 53776.67         | 26090.77         | 2389.31          | 48894.44         |
| 22F          | 11356.79         | -5918.29         | 29478.62         | 13968.83         | -4707.23         | 31272.73         |
| 23A          | 19583.86         | 2091.42          | 36390.54         | 16430.84         | -1658.94         | 34425.99         |
| 3            | 4204.09          | -10402.1         | 18479.71         | 7894.13          | -7770.29         | 22603.41         |
| 31           | 9875.27          | -11992.4         | 31522.79         | 3307.89          | -21515.5         | 26206.01         |
| 6A           | -4723.36         | -25570.3         | 16771.78         | -1870.31         | -24190.9         | 19805.18         |
| 6D           | -7461.26         | -28554.4         | 14396.92         | -15199.3         | -37823.2         | 7751.2           |
| 7F           | 24685.63         | 3471.88          | 46572.29         | 23255.71         | 1374.87          | 44902.99         |
| 8            | 9737.81          | -3884.88         | 23393.2          | 13956.39         | -1263.67         | 28318.91         |
| 9N           | 14296.32         | -2889.44         | 31184.56         | 12904.55         | -5848.54         | 30327.91         |
| Undefined*** | 2907.8           | -9633.08         | 15320.17         | 1982.93          | -12155.3         | 14910.33         |

\***Adjusted coefficient:** adjusted for human immunodeficiency virus (HIV) status and age group

\*\***HDI:** Highest Density Interval of posterior distributions with "-L" = lower bound and "-H" = upper bound

\*\*\***Undefined serotypes** include pool G serotypes (29, 34, 35, 42 and 47), non-typables and serotypes not distinguishable by polymerase chain reaction

**S6 Table** Associations of serotypes with TNF- $\alpha$  concentrations

| Serotype     | Univariate       |                  |                  | Adjusted*        |                  |                  |
|--------------|------------------|------------------|------------------|------------------|------------------|------------------|
|              | coefficient      | HDI-L**          | HDI-H**          | coefficient      | HDI-L**          | HDI-H**          |
| 10A          | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> |
| 12F          | 1.42             | -1.21            | 4.04             | 2.34             | -0.77            | 5.17             |
| 14           | 1.59             | -1.68            | 4.76             | 2.22             | -1.22            | 5.58             |
| 15B/C        | 2.16             | -0.68            | 5.11             | 2.71             | -0.56            | 5.76             |
| 16F          | 0.55             | -3.36            | 4.67             | 1.12             | -3.09            | 5.31             |
| 18A          | 5.73             | 1.65             | 9.88             | 6.22             | 2.08             | 10.31            |
| 19A          | 1.2              | -2.08            | 4.4              | 1.02             | -2.36            | 4.46             |
| 19F          | -0.9             | -4.18            | 2.29             | 0.07             | -3.69            | 3.53             |
| 22A          | 0.18             | -3.79            | 4.28             | 1.46             | -3.28            | 6.28             |
| 22F          | 0.24             | -2.91            | 3.65             | 0.77             | -2.61            | 4.17             |
| 23A          | -0.86            | -4.11            | 2.38             | -0.99            | -4.41            | 2.53             |
| 3            | 0.31             | -2.32            | 2.99             | 1.02             | -2.02            | 4.08             |
| 31           | 2.13             | -1.9             | 6.05             | 3.4              | -1.3             | 8.18             |
| 6A           | 3.48             | -0.46            | 7.41             | 4.02             | -0.2             | 8.07             |
| 6D           | -2.48            | -6.42            | 1.57             | -3.21            | -7.5             | 1.21             |
| 7F           | 0.67             | -3.46            | 4.57             | 0.31             | -4.01            | 4.37             |
| 8            | 1.37             | -1.28            | 3.88             | 2.14             | -0.61            | 4.96             |
| 9N           | -0.09            | -3.3             | 3.1              | -0.12            | -3.62            | 3.57             |
| Undefined*** | -0.02            | -2.38            | 2.45             | 0.18             | -2.42            | 2.82             |

\***Adjusted coefficient:** adjusted for human immunodeficiency virus (HIV) status and age group

\*\***HDI:** Highest Density Interval of posterior distributions with "-L" = lower bound and "-H" = upper bound

\*\*\***Undefined serotypes** include pool G serotypes (29, 34, 35, 42 and 47), non-typables and serotypes not distinguishable by polymerase chain reaction

**S7 Table** Associations of serotypes with case fatality

| Serotype     | Univariate       |                  |                  | Adjusted*        |                  |                  |
|--------------|------------------|------------------|------------------|------------------|------------------|------------------|
|              | coefficient      | HDI-L**          | HDI-H**          | coefficient      | HDI-L**          | HDI-H**          |
| 10A          | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> | <i>Reference</i> |
| 12F          | -0.33            | -2.68            | 1.86             | -0.49            | -2.91            | 1.73             |
| 14           | -1.97            | -6.09            | 0.64             | -1.4             | -5.92            | 1.76             |
| 15B/C        | 2.94             | 0.34             | 7.35             | 2.52             | -0.09            | 6.69             |
| 18A          | -1.44            | -5.79            | 1.52             | -1.83            | -6.05            | 1.17             |
| 19A          | 1.91             | -1.18            | 6.3              | 1.69             | -1.53            | 6.12             |
| 19F          | -1.51            | -5.89            | 1.5              | -1.83            | -6.18            | 1.28             |
| 22F          | 1.9              | -1.22            | 6.19             | 1.57             | -1.32            | 5.79             |
| 23A          | 0.22             | -2.11            | 2.72             | -0.6             | -3.32            | 1.98             |
| 3            | 0.74             | -1.11            | 2.61             | 0.41             | -1.48            | 2.49             |
| 6A           | 1.84             | -1.1             | 6.04             | 1.53             | -1.47            | 5.94             |
| 7F           | -1.47            | -5.95            | 1.53             | -0.68            | -5               | 2.98             |
| 8            | -0.89            | -2.66            | 0.8              | -0.65            | -2.73            | 1.24             |
| 9N           | -1.51            | -5.72            | 1.57             | -0.7             | -5.13            | 2.91             |
| Undefined*** | -0.67            | -2.28            | 0.84             | -1.44            | -3.17            | 0.28             |

\***Adjusted coefficient:** adjusted for human immunodeficiency virus (HIV) status and age group

\*\***HDI:** Highest Density Interval of posterior distributions with "-L" = lower bound and "-H" = upper bound

\*\*\***Undefined:** include pool G serotypes (29, 34, 35, 42 and 47), non-typables and serotypes not distinguishable by polymerase chain reaction