Table 1: Eligibility and exclusion criteria

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| **Inclusion** | **Exclusion** |
| ●       Human respiratory syncytial virus studies in adults  ●        Severity of RSV infection assessed  ●       Biological marker investigated  ●      Studies written in English, French, Spanish, Italian or Portuguese | ●        Studies in animal models  ●        *In vitro* studies  ●        Studies exclusively in children  ●       Studies of treatment, diagnostics or epidemiology of RSV infection  ●      Absent definition of disease severity  ●    Studies without a definitive RSV diagnosis  ●     Studies focusing on viral characteristics.  ●     Literature reviews |
|  |  |

Table 2: Summary of RSV Biomarkers in Adults

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| **Marker of Infection Severity** | | **Marker of Susceptibility for Infection** | |
| **Systemic Markers** | **Airway Markers** | **Systemic Markers** | **Airway Markers** |
| Low RSV neutralizing antibody titer in serum [18] (Trend P=0.07) | Low levels of RSV CD8 + T cells in BAL [28] (P=0.0142 r= -0.691) | Low RSV neutralizing antibody titer in serum **[**10] (P≤ .028) [12] (P = 0.008 and P = 0.01 for RSV/A and RSV/B respectivley [13] (P=0.018) [14] (P = 0.04) | Low IgA to RSV F, Ga + Gb proteins in nasal secretions [22] (r = .58–.76; P = .0001) |
|  | High levels of IL-6 in airway [38] (P < 0.001) | Low IgG to F, Ga + Gb RSV protein levels in serum [22] (r = .54–.80; P = .0001) [14] (only F-Protein P = 0.02) | Low IgA to RSV in nasal mucosa [15] (P < 0.05) [19] (P=0.292) |
|  | High levels of IL-8 in airway [38] (P= < 0.001) |  | Low IgA to RSV F-Protein in nasal mucosa [15] (P < 0.05) |
|  | High levels of MPO in airway [38] (P= < 0.001) |  |  |
|  | High Viral Load [28] (P=0.003) [33] (P=<0.05) [34] [35] (P=0.0340) [37] (P =0.011) |  |  |
|  | Viral shedding in nasal secretions for longer [20] (13.1 vs 9.8 days; P = 0.003) |  |  |
|  | Low levels of IgA to RSV Ga + Gb in nasal mucosa [20] (Ga P=0.003 Gb P <0.0001) [34] (P=0.03) |  |  |
|  | Higher levels of nasal IL-6 [20] (OR 2.2 (1.2-4.2) P=0.01) and MIP-1α [20] (OR 9.1 (0.95 – 87.6) P= 0.06) |  |  |

Table 3: Study Characteristics

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| **Author, year** | **Prospective Study** | **Natural Infection** | **Healthy Controls / Younger Adults Included** | **High Risk / Co-Morbid Adults Included** | **Older Adults Included** |
| Falsey AR, 1999 [9] | Yes | Yes | Yes | Yes (nursing home eligible but living in the community) | Yes |
| Cherukuri A, 2013 [11] | Yes | No | Yes | No | Yes |
| Falsey AR, 1998 [12] | Yes | Yes | Yes | Yes (nursing home eligible but living in the community) | Yes |
| Walsh EE, 2004 [13] | Yes | Yes | Yes | Yes (Underlying symptomatic cardiopulmonary conditions) | Yes |
| Lee FE-H, 2004 [14] | Yes | No | Yes | No | No |
| Habibi MS, 2015 [15] | Yes | No | No | No | No |
| Falsey AR, 1992 [18] | Yes | Yes | No | Yes (Nursing Home Residents) | Yes |
| Bagga B, 2015 [19] | Yes | No | Yes | No | No |
| Walsh EE, 2013 [20] | Yes | Yes | Yes | Yes | Yes |
| Walsh EE, 2004 [22] | Yes | Yes | Yes | Yes (CHF / COPD) | Yes |
| Jozwik A, 2015 [28] | Yes | No | Yes | No | No |
| Duncan CB, 2009 [36] | Yes | Yes | Yes | Yes | Yes |
| Lee N, 2015 [37] | Yes | Yes | Yes | Yes | Yes |
| Wilkinson TM a, 2006 [38] | Yes | Yes | No | Yes (all patients had COPD) | Yes |

Table 4– Future Research Options

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| --- | --- |
| **Limitations with current research** | **Possible future research options** |
| Challenge Studies have previously been only in young healthy adults | Challenge studies in older adults and co-morbid populations |
| Mainly upper airway studies have been performed in the observational groups | Lower airway sampling in infected adults is needed with comparison between upper and lower airway biomarkers |
| Virus has been found at multiple timepoints in the same patient. It is not known if this is RSV recurrence or ‘chronic infection’ | Genotyping of RSV found in the same patient at multiple timepoints may confirm if infection with a new strain is occurring or if the virus is not being cleared |
| Viral clearance is poorly understood | Investigate which host or virologic factors influence the rate of viral clearance and disease severity, e.g. the kinetics of viral clearance and anti-viral immune responses. |
|  | Investigate the role of pre-f antibodies in disease susceptibility in adults |
|  | Why is infection severe in some populations and mild in others and are the kinetics of viral clearance distinct between these groups |