Experimental Respiratory Syncytial Virus Infection in Adults 60-75 years

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BACKGROUND

The RSV human challenge model has utility for vaccine/drug efficacy testing, however models including target populations are lacking. We present safety and disease outcomes from a novel challenge study in 60 to 75-year old volunteers.

STUDY DESIGN

Twenty- four male and female subjects aged 60 to 75 years ("older"), with no at-risk comorbidities for RSV, were enrolled without selection of low-level antibody status into an in-patient challenge study design. Following screening subjects were admitted to clinic on day -2, inoculated intranasally with RSV Memphis 37b on day 0 and discharged no earlier than day 12.

Throughout the study safety monitoring, viral shedding, symptoms, and nasal discharge were measured. The infection and disease profiles were compared to a historical cohort of 41 infected 18 to 55-year-old heathy subjects ("younger") with low baseline levels of antibodies to RSV.

Baseline characteristics that were significantly different between the younger an older study groups are outlined in table 1.

Table 1. Demographic characteristics significantly different between older and younger groups.

Baseline characteristics	18-55 (n=58)	60-75 (n=24)	p value *
Median age (range min,max)	25 (18,45)	63 (60,74)	< 0.0001
Female, n(%)	19 (33%)	6 (25%)	< 0.01
Median Weight (kg) (min,max)	75.5 (53.2,104.4)	84.3 (52.4,103.8)	< 0.05
Median BMI (kg/m^2) (min,max)	24.0 (18.9,31.9)	27.6 (20.7, 33.0)	< 0.01
Median neutralisation titre baseline (95% CI)	810 (810,1403)	2430 (1403,2430)	< 0.0001
Smoking (median pack yrs) (min,max)	0 (0,5)	0 (0,8)	<0.001

* Unpaired, Mann-Whitney test (no adjustment for multiple comparisons)

RESULTS

Detectable viral shedding was present in 12 of 24 older subjects (50%), with 10 of 24 subjects (42%) meeting the protocol definition of "quantifiable" lab-confirmed infection. There were no SAEs and all AEs were of mild-to-moderate severity. While infected older subjects had similar maximum levels of viral loads, symptoms, and nasal discharge when compared to younger subjects (Figure 1, right column), the time course plots show a different overall profile of disease. This different group mean profile is a reflection of more subjects in the older group having a later onset. As shown in Figure 2, older subjects had a significantly protracted incubation period with a rapid subsequent rise to peak viral load (delayed onset of PCR (median ~ 4 days later , p<0.0001*), a longer time to peak PCR (median ~ 1 day later, p<0.01*) and a shorter time from onset to peak PCR (median ~2 days earlier, p<0.05*). A higher proportion of older infected subjects met the more severe endpoints than younger subjects, with 80% of older subjects (Table 2) having moderate or higher illness (≥ grade 2 symptom). There was a trend towards greater nasal discharge weight in older subjects that requires confirmation in a larger n sample size.

Figure 1. Comparison of viral titre, total symptom score and mucus weight in older (red) vs younger (blue) subjects

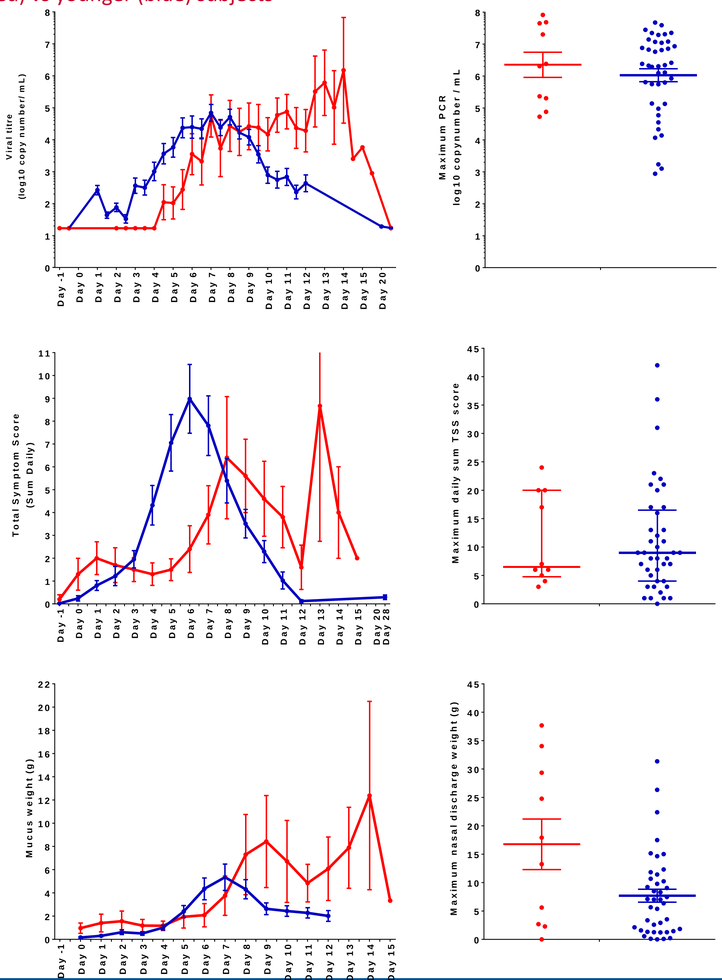

Figure 2. PCR virology differences in older (red) vs. younger (blue) subjects.

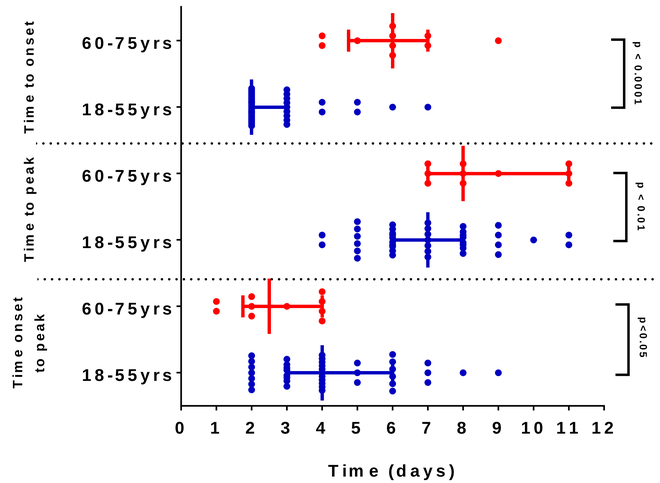

Table 2. Mild moderate and sever disease severity in older subjects.

60-75 YEAR OLD INFECTED SUBJECTS 2 quantifiable (>LLOQ) within 2 days (10/24, 42%)				
Disease criteria	**All**	**Infected**	**Uninfected**	**p-value ***
Mild disease: Any ≥1 symptom on any occasion	20 (83%)	10 (100%)	10 (71%)	ns
Moderate disease: Any ≥2 grade symptoms on any occasion	10 (42%)	8 (80%)	2 (14%)	< 0.01
High disease: Any ≥2 grade symptoms on ≥ 2 separate occasions	5 (21%)	5 (50%)	0 (0%)	< 0.01
Culturable infection: ≥1 cell culture positive supported by PCR	7 (29%)	7 (70%)	0 (0%)	< 0.001

* Fishers exact t test, two sided.

CONCLUSIONS

- This novel RSV challenge of 60-75-year-old volunteers was considered safe and induced an appropriate level of disease for which to progress with assessment of vaccines and drugs targeted at the 60-75-year-old population.
- Interestingly older subjects had a significantly protracted incubation period and rapid rise to peak viral load (neither correlating with baseline neutralisation titre).
- In this pilot study there was no evidence of pre-existing neutralisation antibody levels affecting susceptibility to infection or severity of disease.