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RSV Immunity, Durability, and Reinfection

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Agenda

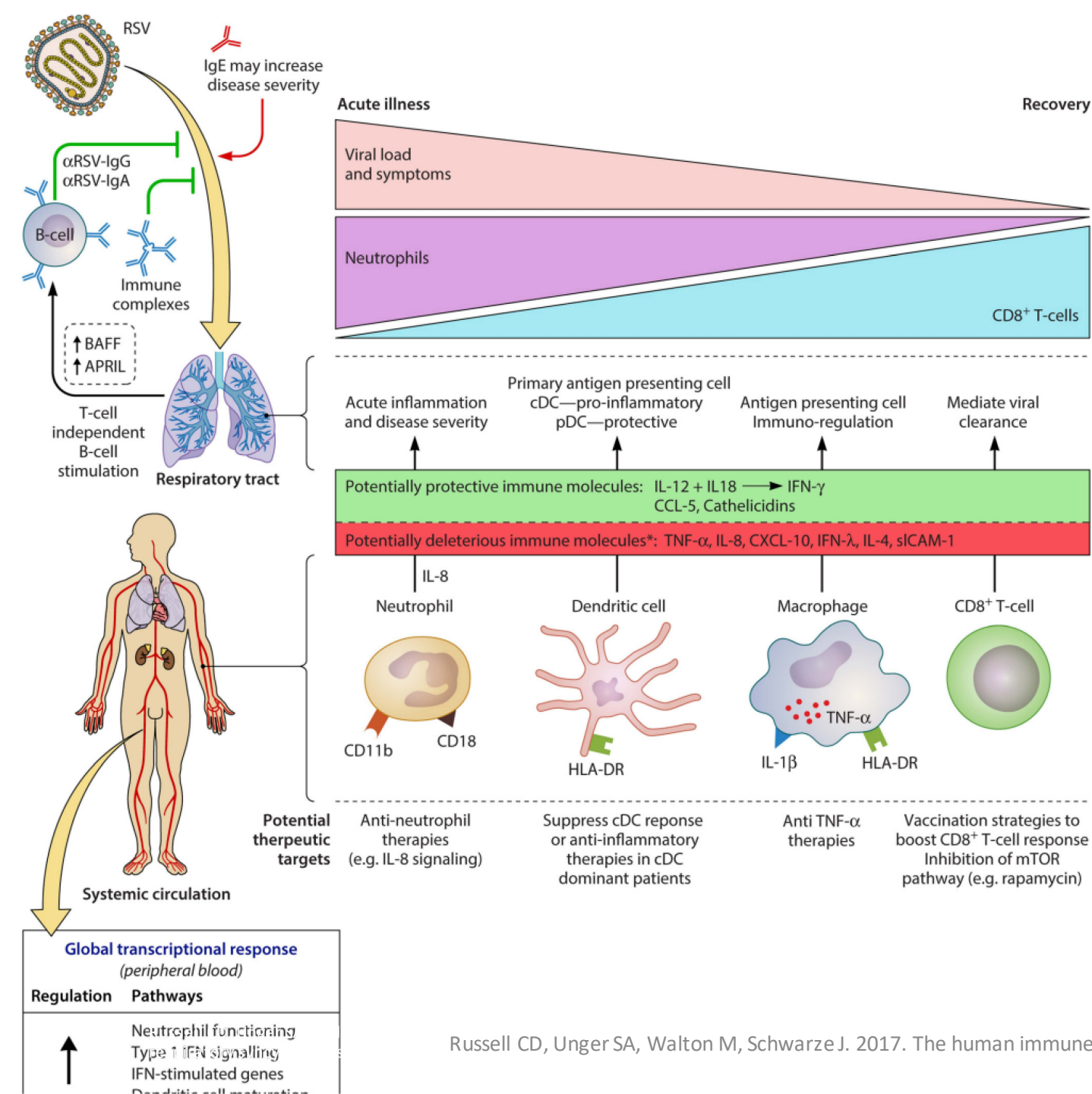
- Overview of immune response to infection
- Pre-existing immunity – Young vs Older Adult
- Infection in Adults
- Infection in Frail Older Adults
- Durability of Immune Response
- Proximity of Reinfection
- Conclusions

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An image showing immune response to infection as stated on slide # 4.

- Summary of the human immune response to RSV and potential novel therapeutic targets. The roles of major cell types (neutrophils, dendritic cells, macrophages, CD8 T cells, and B cells) are summarized, in addition to key antibody, cytokine, chemokine, and other immune molecule responses. Major transcriptional changes (in peripheral blood) of immune-related pathways are shown. The deleterious role of neutrophilic inflammation and the protective role of CD8 T-cell-mediated viral clearance are emphasized. Finally, we highlight areas where novel therapeutic interventions could potentially modulate the immune response in favor of the host. 1, immune cell recruitment to the respiratory tract; *, association with increased disease severity.



- Initial strong neutrophil response mediated by interleukin-8 (IL-8)
- Dendritic cells migrate to the lungs
- An initial systemic T-cell lymphopenia is followed by a pulmonary CD8 T-cell response, mediating viral clearance.
- Humoral immunity to reinfection is incomplete, but RSV IgG and IgA are protective and reduce viral replication.
- IFN γ has a strongly protective role, and a Th2-biased response may be deleterious.

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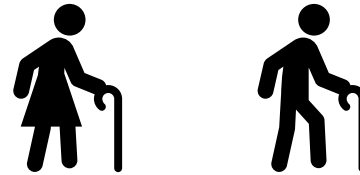
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Pre-existing Immunity

Younger vs. Older Adults



- 30 young adults
- 20-30 years of age
- median age 26 years

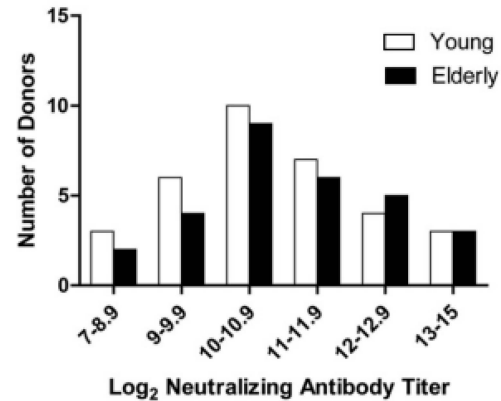


- 30 elderly adults
- 65-85 years of age
- median 74 years

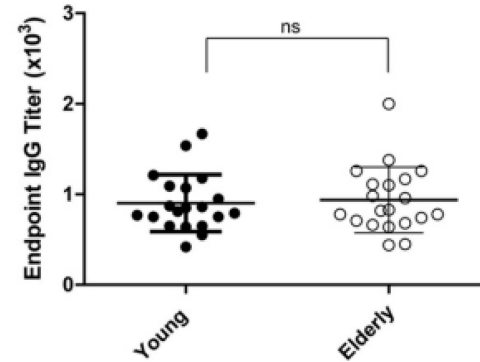
An image showing RSV-specific antibodies as stated on slide # 9.

- Equivalent RSV-specific antibody levels in plasma of young and elderly donors. (A) RSV-specific antibody titers in plasma from young ($n = 30$) and elderly ($n = 30$) donors were compared by microneutralization of GFP-RSV A2 virus. (B) F-specific IgG ELISA. (C) Correlation analysis between neutralizing antibody titers and F-specific IgG titers. (D) RSV F-specific and total IgA titers in nasal washes of young ($n = 10$) and elderly ($n = 20$) adults.

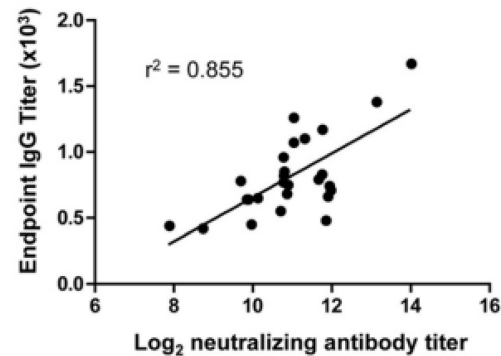
A. RSV A2 Neutralizing Antibody Titers



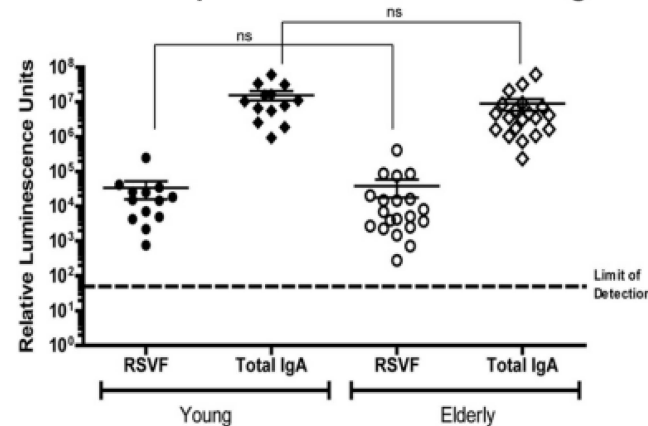
B. RSV F-Specific Plasma IgG



C. RSV F-Specific IgG Versus RSV Neutralizing Antibody Titers



D. RSV F-Specific and Total Nasal Wash IgA

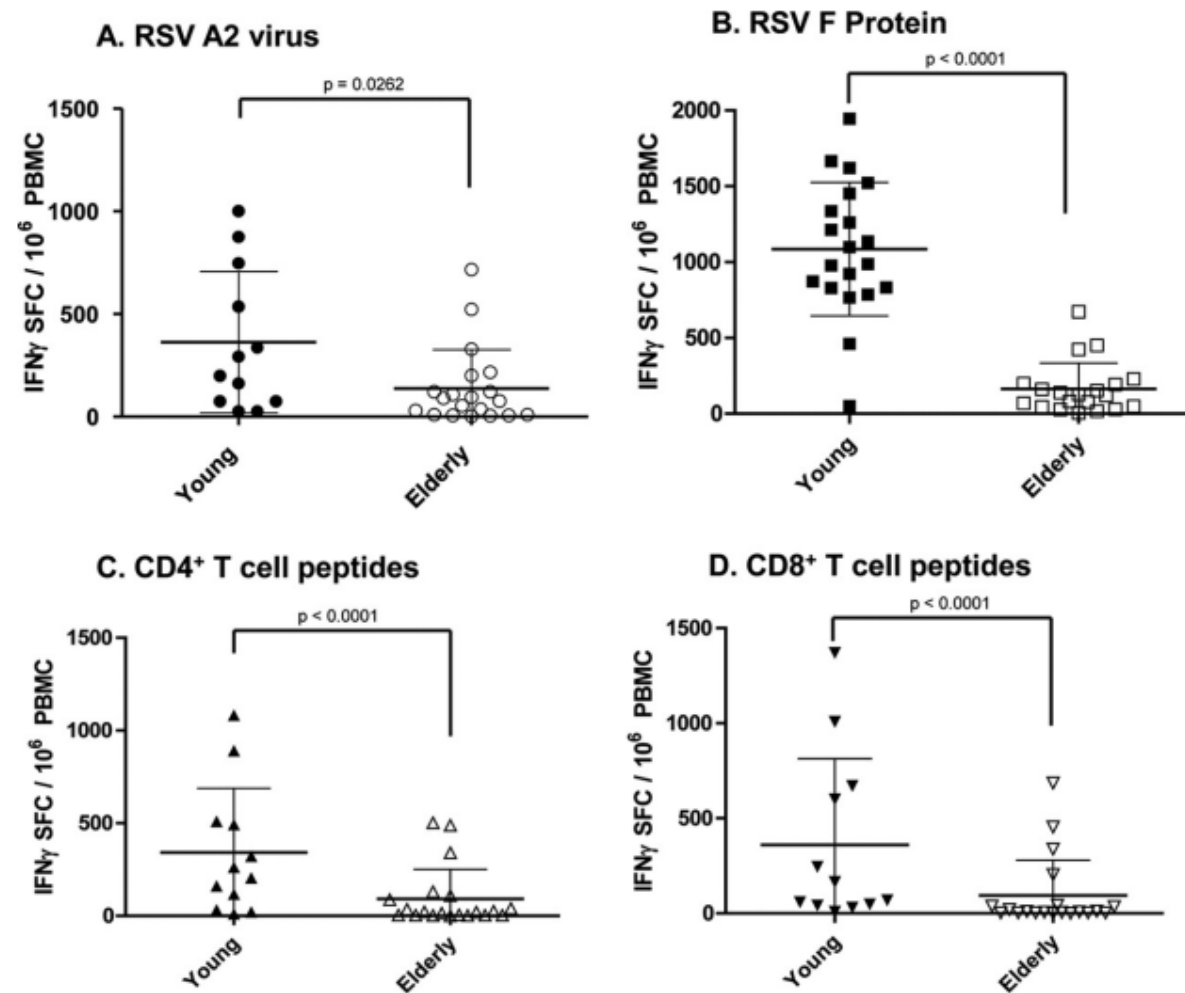


- Similar Antibody titers in young and older adults.
- No significant difference in serum IgG or Nasal Wash IgA

An image showing interferon gamma responses to RSV stimulation as stated on slide #11.

- Elderly have significantly lower numbers of RSV F-specific IFN--producing cells. PBMC from young and elderly donors were stimulated *ex vivo* using (A) wt RSV A2 at 1 PFU/10 cells (*n*12 young and *n*20 elderly), (B) 5g/ml of RSV F protein (*n*20 young and *n*20 elderly), (C) 2g/ml of RSV F-specific CD4 T cell peptide pools (*n* 12 young and *n* 12 elderly), or (D) 2 g/ml of RSV F-specific CD8 T cell peptide pools (*n* 12 young and *n* 12 elderly). The IFN- secreted by T cells was measured by ELISPOT assay, and data are expressed as spot-forming cells (SFC)/10⁶ PBMC.

- Significant reduction in IFN γ response in elderly compared to young



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Pre-existing Immunity and risk of infection

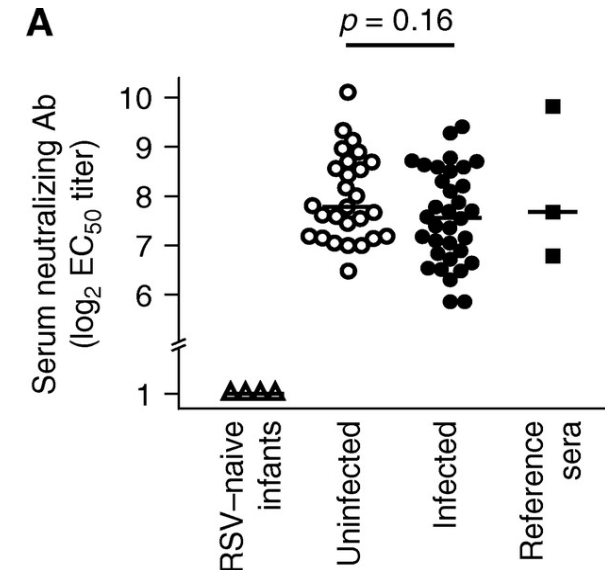
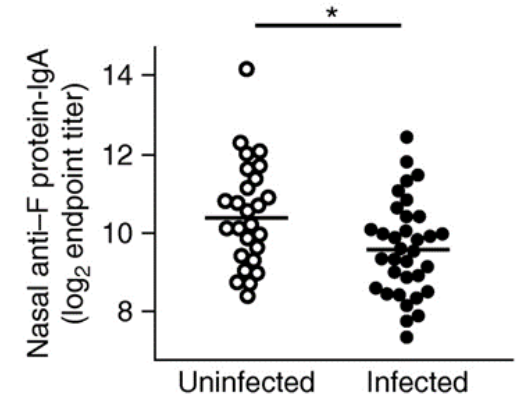
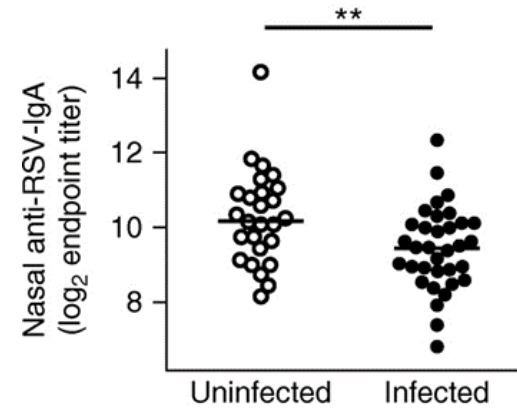
- Challenge Study in US
- 61 healthy adults 18-55 years of age
- Challenged with live RSV
- Serum and mucosal antibodies measured pre and post infection
- 34 (36%) became infected; 28 were symptomatic (68%)

An image showing risk of infection as stated on slide # 15.

- Respiratory syncytial virus (RSV)–specific nasal IgA is a superior correlate of protection to serum neutralization titer. (A) Serum neutralizing antibody (Ab) was determined by plaque reduction neutralization and nasal IgA by ELISA. Baseline serum neutralizing (*top*), nasal IgA against whole RSV (*middle*), and nasal anti-RSV fusion F protein (*bottom*) Ab levels in uninfected (*open circles*) versus infected (*solid circles*) subjects are shown. Serum neutralization includes four infant samples (*open triangles*) and three reference serum standards (*solid squares*; Wyeth 06937, 06938, and 06939). *Horizontal bars* indicate the median.

Pre-existing humoral immunity and risk of infection

- Lower IgA antibody levels are more likely associated with infection
- No difference seen in serum neutralizing antibody

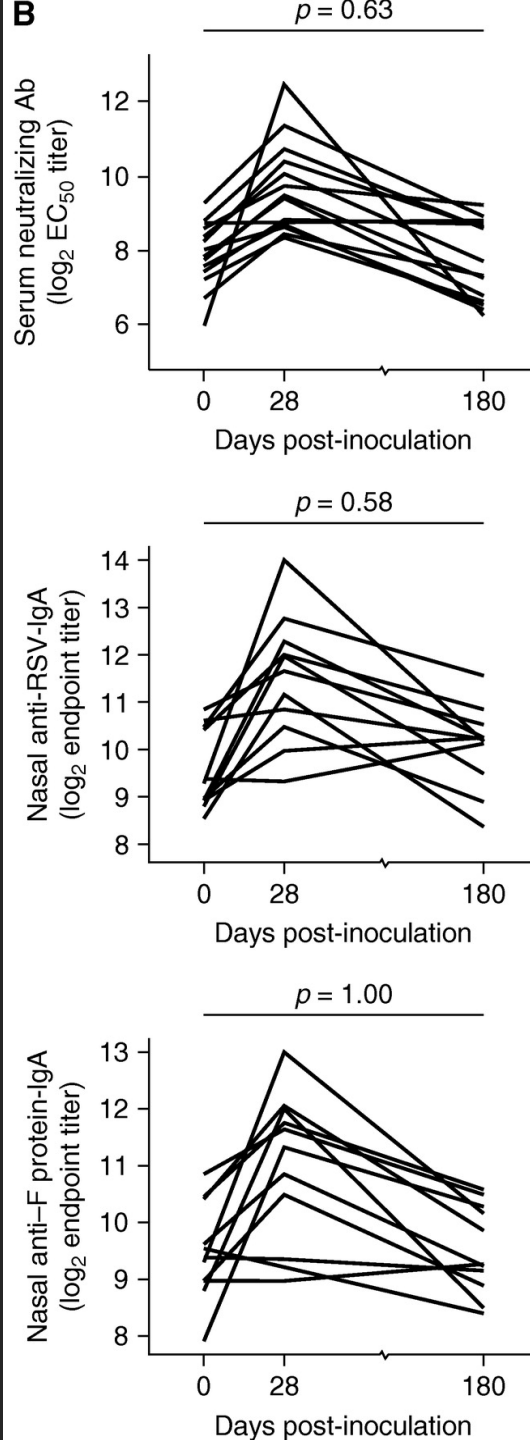


An image showing an increase in serum and nasal antibody post-infection that is not maintained as stated on slide # 17 .

Serum and nasal antibody (Ab) increase after infection but are not maintained. Healthy adult volunteers were challenged intranasally with respiratory syncytial virus (RSV) A M37. Serum and nasal lavage was taken at baseline and 28 days postinoculation. A subset of subjects returned for further blood and nasal sampling 6–12 months later (nominally Day +180). Serum neutralizing Ab was determined by plaque reduction neutralization and nasal IgA by ELISA. (B) Individual plots showing trend in Ab levels at baseline and Days +28 and +180. *P* values for unpaired Mann-Whitney Wilcoxon *U* test are shown. EC50 = half-maximal effective concentration. ****P* < 0.001.

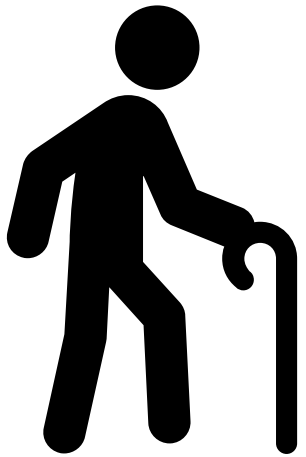
Antibody Levels Pre- and Post-RSV infection

- Infection associated with rise in both serum and IgA antibodies after infection
- Antibody levels usually return to pre-infection levels by 6 months



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Susceptibility to RSV infection in Frail elderly

- Cohort of frail elderly, older adults
- Followed for over a 26-month period
 - February 1992 – April 1994
- 28 RSV infections were diagnosed.

	Infected	Uninfected
Mean Neutralizing Antibody Levels RSV A	12.4 ± 2.2	14.2 ± 2.2

- (p <0.008)

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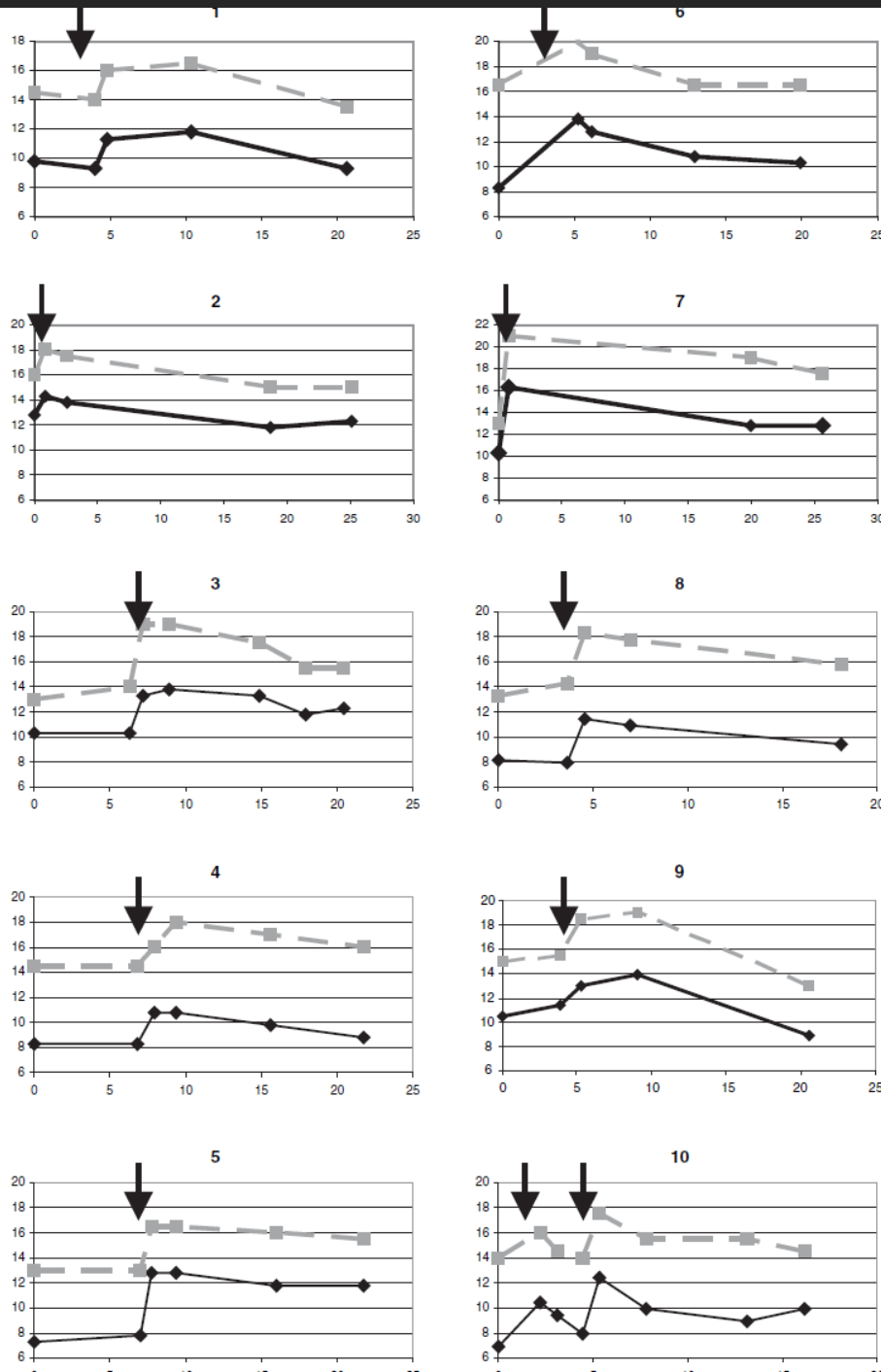
An image showing decline of anti-RSV antibodies as stated on slide #22.

- Representative graphs from 10 of 20 RSV infected subjects showing antibody titers over the months of study. The solid black line indicated MNA titers and the gray broken line indicates EIA F titers. Black arrows indicate time of RSV infection.

Antibody Decay

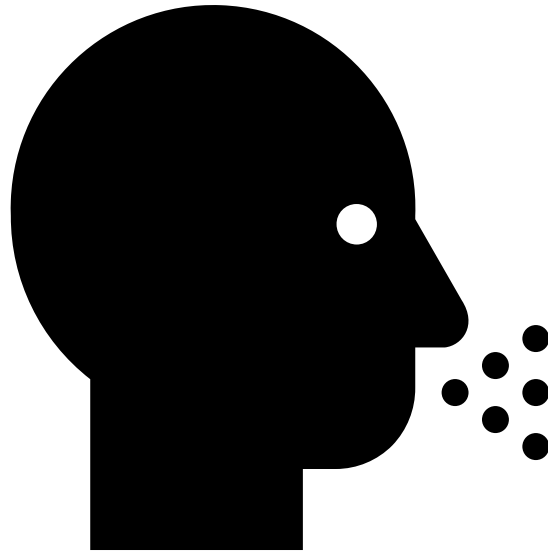
- RSV infected subjects showing antibody titers over the months of study.
- The solid black line indicated MNA titers and the gray broken line indicates EIA F titers.
- Black arrows indicate time of RSV infection.
- Boost in serum and binding antibodies is relatively short lived.

Log 2
Titer



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Reinfection

- Evasion of innate immunity
 - Suppression of IFN-mediated antiviral responses
- Failure to protect against reinfection
 - Even though genetic diversity is not extreme, durability of immune response is inadequate

Adult Challenge Study

- 15 RSV infected individuals were identified
- Challenged with RSV repeatedly after natural infection
- Highest rate of reinfection occurred 2 months after natural infection

Time of challenge (no. of subjects)	% infected	Viral shedding		
		% shedding	Mean duration (days)	Mean peak titer (log ₁₀ TCID ₅₀ /ml)
Natural infection (15)	100	100	4.7	3.5
2 months (15)	47	47	4.6	3.4
4 months (10)	30	0	0	0
8 months (14)	29	21	4.1	2.5
14 months (12)	25	8	1	1.2
20 months (11)	27	27	2	1.7
26 months (10)	30	30	1	0.7

How often a person be re-infected?

- 10 (67%) were re-infected at least once more after natural infection in the 26-month period
- 7 (47%) were infected 2 or more times
- The highest reinfection time was at the first challenge time point.

Subject	No. of reinfections after natural infection	Months between			
		Natural and first reinfection	First and second reinfection	Second and third reinfection	Third and fourth reinfection
1	4	2	2	4	6
2	4	2	2	10	8
3	3	2	2	16	
4	2	8	18		
5	2	8	12		
6	2	2	6		
7	2	14			
8	1	2			
9	1	8			
10	1	2			
11	1				
12	0				
13	0				
14	0				
15	0				

NOTE. Mean and median values: between natural infection and first reinfection, 5 and 2 months, respectively; first and second reinfection, 8.6 and 4; second and third, 10 and 10; and third and fourth, 7 and 7.

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Conclusions

- Natural RSV infection does not provide durable or complete protection from re-infection.
- Anti-RSV antibodies return to pre-infection levels within 6 months after infection
- Reinfection can occur within 2 months of last infection.
- Older adults have weaker IFN γ responses to RSV than younger adults do, likely making older adults more susceptible to infection and to severe infection.

Questions

