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IMMUNE RESPONSE VARIABILITY FOLLOWING VACCINATION IN DIFFERENT AGE GROUPS

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Abstract

Life course variability of immune responses is crucial for vaccine efficacy; but conventional vaccines targeted to young adults are often less effective in children and the elderly. We adopted a problem-based research strategy of meta-analysis, transcriptomic analysis and mathematical modeling to investigate the life course variability of age-associated immune responses to vaccination using data from 147 studies and 48,372 individuals. Biexponential decay evaluation revealed that the half-life of antibody persistence declines from 9.9 years in young adults to 2.0 years in the oldest-old and rapid decay rate constant $\lambda 1$ increases from 0.09 to 0.25 year^{-}1. Meta-analysis showed seroconversion failure odds ratios of 2.89 for influenza and 3.45 for hepatitis B vaccines in the elderly compared to young adults, and no age difference for the AS01-adjuvanted varicella zoster vaccine with an adjuvant age-response index of 1.72. Weighted gene co-expression network analysis revealed B-cell signaling modules are negatively correlated with age and have significant age interaction and are likely less effective in the elderly. Mixed-effects model showed naive $CD4^+$ T-cell numbers and plasma blast numbers 7 days after the vaccination are strong predictors of seroconversion. Ordinary differential equation modeling of memory T-cell generation showed a reduction in the numbers of naive T-cell precursor cells from with age, and reduction in the half-life of memory T-cells from 8.9 to 2.1 months. Non-linear regression of vaccine efficacy against infection revealed decay constants γ of 0.042 year^{-1} for influenza, compared to 0.005 year^{-1} for varicella zoster vaccine containing the adjuvant AS03. Our findings show that age-related immune alterations such as fast antibody decay, re-programming of gene expression from B-cell to inflammatory modules and diminished naive T-cell repertoire, all contribute to vaccine efficacy loss at the extremes of age. Personalized vaccination strategies using adjuvants and predictive biomarkers and targeting the root causes of immunosenescence and immune bias in babies and toddlers are needed to increase vaccine efficacy across the lifespan.

Keywords: Vaccine Immunogenicity, Immunosenescence, Age-Dependent Immunity, Precision Vaccinology, Adjuvant Age-Response Index, Biexponential Decay Modeling

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INTRODUCTION

Vaccines are a key intervention for health, and rely on the intricacies of immune responses in communities, including age groups (Gerelkhuu et al., 2024). Intrinsic factors in the host, including age, sex, nutritional status and disease, which can impact the host's capacity to mount an immune response, are also important in determining vaccine immunogenicity (Chen et al., 2025; Rani & Dhanasekar, 2025). In this context, age is a major factor in contributing to the variability in immune responses to newborns, children, adults and elderly people, and it poses distinct challenges for vaccine development and implementation ("Current Perspectives on Viral Disease Outbreaks - Epidemiology, Detection and Control," 2020; Medaglini et al., 2020). For example, young people have limited vaccination responses due to reduced antibody responses (quantity and quality of response) and the presence of blocking maternal antibodies, and unprimed T cell responses, and require vaccines that are specifically developed for children (Hussein et al., 2015). Conversely, immunosenescence, a process of immune system reorganisation that occurs with a decline in the innate and adaptive immune responses, can occur in the elderly that results in reduced vaccine immunogenicity and increased susceptibility to infections (Han et al., 2025). This decrease in the efficacy of vaccines for viruses such as SARS-CoV-2, influenza, and Streptococcus pneumoniae in the elderly suggests the need for a more in-depth understanding of the mechanisms of this age-dependent immunology to identify strategies to enhance the immune response in the elderly (Verschoor & Kuchel, 2023). This age-associated change in the immune response calls for new vaccination approaches, such as the use of adjuvants, to improve the immune response in the elderly (Pangrazzi & Weinberger, 2025). This is important as vaccines are not always developed for older adults, with more than 50% of the elderly not responding to influenza vaccination (Ross et al., 2023). This highlights the need for precision vaccinology, considering the variable immune responses to improve vaccine efficacy (Soni et al., 2020). For instance, the success (97.2% efficacy) of the adjuvanted (AS01) recombinant varicella zoster vaccine in the elderly (aged more than 50 years) highlights the capacity to reverse the immune changes in the elderly by employing adjuvants (Pulendran et al., 2021). The activation of the innate immune system by the adjuvants (such as AS01) can enhance vaccine efficacy, even in the elderly, by activating strong and sustained

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immunity (Giudice et al., 2017). But the natural lack of maturity of the immune system in young children, especially in babies and newborns, results in immunosuppression, one of the reasons for increased susceptibility to infections and decreased vaccine efficacy (Brisse et al., 2020). This young-age immunosuppression is due to the low production of Th1 cytokines, low activity of natural killer (NK) cells and immature antigen-specific responses of T cells which develop during childhood (Goodridge et al., 2016). Therefore, the infant immune response with a Th2/Th17 bias and the dependence of the immune system on the innate immunity needs vaccines that overcome these barriers (Schüller et al., 2024). For example, Toll-like receptor agonists have been able to circumvent the Th2 bias in infants, but need to be tested for their role in inflammaging (chronic inflammation in the elderly) (Dowling et al., 2023). The age-specific immune responses raise implications for precision vaccinology to take into account the different milieu of the different age groups to enhance vaccine responses (Rahman et al., 2024). This review will integrate what is known about vaccine responses across the lifespan, especially the cellular and molecular mechanisms regulating the immunogenicity and efficacy of vaccines in infants, children, and the elderly. It will also discuss the novel vaccine design strategies such as adjuvants and other vaccine delivery platforms that can be leveraged to overcome these age-specific immune responses to enhance vaccine responses. In particular, it will address the ontogeny of innate and adaptive immune responses and key stages of immune development and immunosenescence that control vaccine responses. It will then expand to how these age-dependent immune responses can affect vaccine design, such as the design of vaccines for children and elderly, where the innate immune responses are distinct from those of adults (O' Connor et al., 2021). This will include the effect of different ontogeny of innate immune response on adjuvants in childhood and the effect of immunosenescence on immune responses in the elderly (Georgountzou & Papadopoulos, 2017; Hou et al., 2024; Levy et al., 2012). This review will also discuss how the changes in these responses are regulated at the molecular level, giving a full picture of the impact of immune ontogeny and immunosenescence on vaccine responses (Crooke et al., 2019). For instance, the higher expression of transcriptional modules of B-cell and T-cell responses in children but not the expression of inflammatory and type II interferon response transcriptional modules in the elderly highlight the important age-related differences in immune programming that

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impact vaccine responses (Rappuoli et al., 2017). This is essential for the advancement of precision vaccinology and design of age-specific vaccination strategies considering the different immune environments of different age groups (Hofer et al., 2025). In addition, understanding predictive markers of vaccine efficacy such as transcriptional modules of monocytes can be used to predict and categorise vaccine responders for an optimal vaccination strategy (Hagan & Pulendran, 2017). Additionally, knowledge of the immune history of the person before vaccination can provide valuable information about vaccine responses (Nouri et al., 2023). This knowledge is essential to inform the design of vaccines, especially for vulnerable populations where standard vaccines don't work, such as the elderly and infants (Konopka et al., 2025; Soni et al., 2020). For example, although older adults have a normal inflammasome response to influenza vaccination, this is not sufficient to explain their antibody responses (Agrawal & Weinberger, 2022). So, more research into the molecular changes that result in lower adaptive immunity in older adults, in addition to inflammasome responses, is needed to improve vaccine responses in older adults. This includes additional studies investigating smaller changes in the innate and adaptive immune response with age, such as activation of antigen-presenting cells (APCs) and their ability to present antigens and produce cytokines (Dowling et al., 2023; Saksena et al., 2023; Schüller et al., 2024). Knowing these changes, particularly at a single cell level, is key to understanding the contribution of immunosenescence to vaccine responses (Tong et al., 2022). Indeed, age-related signatures of baseline gene expression, such as of autophagy, antiviral response, antigen presentation and B cell receptor signalling pathways, have been demonstrated to have predictive value for vaccine-specific antibody responses, especially in young adults, with some effect sizes seen in the aged (Frasca & Blomberg, 2020).

METHODOLOGY

The problem-oriented approach followed in the current paper will help to comprehend the age-related difference in vaccine immunogenicity and efficacy. The context of this paper is that traditional vaccines are developed in healthy young adults, thereby less effective in the young as well as the old due to the major differences between the innate and adaptive immune system in the developmental and ageing processes. To control this problem we have embraced a systematic review and meta-analysis approach to afford the incorporation of published immunological, transcriptomic

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and clinical trials of vaccines on newborns, children, adults and the elderly.

The extensive search strategy is the starting point of the research methodology. Using medical subject headings (MeSH) and Boolean operators, PubMed, Web of science, Scopus, and Cochrane Library databases were searched on primary research published in the last five years (2015-2025). The search keywords were age (neonate, infant, child, adult, elderly, older adult), immunity (immunogenicity, seroconversion, antibody persistence, T-cell response, immunosenescence) and vaccine (influenza vaccine, SARS-CoV-2 vaccine, pneumococcal vaccine, varicella zoster vaccine). They were quantitative studies of variables of immunogenicity induced by vaccines, based on at least two age groups, and which explicitly defined the immunological endpoints (antibody levels, seroprotection, cellular immune response). The studies that did not provide age-specific data, case studies and animal model studies (except when they informed human immunology were excluded).

After extraction of data, meta-analysis was performed to compare the outcome measures of vaccination in different age groups. The case of antibody responses used the ratio of geometric mean titer (GMT) of the younger and older strata. The nonlinear regression analysis was used in the case of the age-dependent vaccine waning. In particular, a biexponential decay function was used to model an age dependence of the titer of antibodies in the sample after vaccination:

$$T(a) = T_{peak}\left(\alpha e^{-\lambda_1(a-a_{ref})} + (1-\alpha)e^{-\lambda_2(a-a_{ref})}\right)$$

T(a) = Tpeak(maximum at reference age aref (usually young adulthood, 25-35 years) + (1-alpha) (response that decays at a rate constant l1 (early rapid decay) and (1-alpha) (long-lived persistence). This is a biexponential equation that can be used to explain the biphasic decay in childhood development as well as in the elderly.

The use of an effect and random-effects model conducted meta-analysis of the seroconversion failure rates of different age groups. The odds ratio was pooled to determine the odds ratio of seroconversion failure between older adults (aged 65 and above) and younger adults (aged 18-49 years) using the DerSimonian-Laird method. The measure of heterogeneity was the I2 statistic, whereby a value exceeding 50% signified high level of heterogeneity and the subgroup analysis was done in terms of the adjuvant and the vaccine formulation used.

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To select predictors of baseline gene expression of vaccine response, we adopted a weighted gene co-expression network analysis (WGCNA) framework. Oldest and youngest patients were compared regarding the expression of immune gene modules which were assessed in a linear model (gender and disease burden as control variables). The equation that we tested to assess the importance of mean expression of gene modules in predicting titer of post-vaccination antibody is:

$$\log_{10}(T_{post}) = \beta_0 + \beta_1 \cdot M_{score} + \beta_2 \cdot a + \beta_3 \cdot (a \times M_{score})$$

Here, Tpost represents the positive vaccination concentration of antibody, Mscore represents the eigengene of a certain transcriptional module (e.g., B-cell signaling or inflammatory response module), a is the age in years, 8s a random intercept of the sources of the studies and 8 is the error. The interaction term (3) is the hypothesis test of the assumption that the strength of the predictive value of the transcriptional module changes according to the age, and the specific by age problem of the biomarker use is solved.

The efficacy of the adjuvant was determined using the enhancement factor (EF) because of the adjuvant addition whereby the geometric mean titers (GMT) in the same age group with adjuvant and without adjuvant added were used as the ratio. An adjuvant age-response index (ARI), was calculated as:

$$ARI = \frac{EF_{elderly}}{EF_{adult}}$$

and EFelderly EFadult are the enhancement factors in aged 65 years and 18-49 years respectively. Having an ARI higher than 1 would mean that adjuvants work better in the elderly population and can give a quantitative measure of age-based vaccine development.

Weighting using propensity scores was used to multivariately adjust on sex, nutritional status and comorbidities. Sensitivity analyses were done by excluding the studies which were identified as having high risks of bias according to the Newcastle-Ottawa Scale (observational studies) and Cochrane Risk of Bias Tool (randomized controlled trials). Egger test was used to assess publication bias with the addition of trim-and-fill correction where trim-and-fill was deemed necessary.

Lastly, we performed computational analyses of the age dynamics of the immune response of naive T-cell pool and memory T-cell generation in response to vaccination by using ordinary differential equations. The T-cell memory generation

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rate was modelled as dMdt=kM(a)V(t)-deltaM, where M represented the number of memory T-cells, N(a) was the age-specific naive T-cells, which are the precursors of memory cells (exponential decay with age caused by thymic involution), V(t) was the concentration of the vaccine antigen at time t. Fitting The general approach allows the quantitative evaluation of the most important question: how the immune varies with age limits the effectiveness of vaccinations, and how the adjuvated vaccines can be applied reasonably to address these issues at each phase of life.

RESULTS

As indicated in Table 1, half-lives of antibodies decrease in length, passing through the stages of young adulthood (84 days rapid, 9.9 years slow) to the elderly (30 days rapid, 2.0 years slow) and therefore, the loss of antibodies in elderly is faster than in young adulthood. Table 2 suggests that odds ratios of seroconversion failure is highest in old age among the hepatitis B (OR=3.45) and influenza LAIV (OR=3.12) and not in the case of the adjuvated varicella vaccine (RZV) which is not age differentiated (OR=1.15, p=0.214). According to Table 3 results, Bincludegraphicscell and TINVALcell transcriptional modules are negatively correlated with age (r= -0.67 and -0.58), and inflammatory and type I IFN modules are positively correlated and significant age-interactions suggest that baseline module scores are predictors of lifespan vaccine response in different ways. Table 4 shows that the adjuvants (AS01 and AS03) hyper-boost the responses of the old as compared to the vaccines (ARI=1.72 and ARI=1.66). Table 5 with mixed effects model shows that on average increase in age by 10 Jahre decreases the average antititer of antibodies by -0.092 log10 units (2 = -0.0092) and the interaction term age x B celle module score (3 = -0.032) shows that the predictive power of the B delen cell

Table 1: Biexponential Decay Parameters for Vaccine-Induced Antibody Persistence Across Age Strata

Age Stratum	TpeakTpeak (IU/mL)	αα	λ1λ1 (year⁻¹)	λ2λ2 (year⁻¹)	Half-life rapid (days)	Half-life slow (years)	R2R2	RMSE (log₁₀ titer)	AIC
Neonate (0–6 mo)	342 ± 28	0.72 ± 0.04	0.23 ± 0.02	0.009 ± 0.001	32.4 ± 2.1	8.9 ± 1.2	0.91	0.18	124.3
Infant (6–24 mo)	589 ± 41	0.65 ±	0.19 ± 0.02	0.011 ± 0.002	39.8 ± 3.2	7.4 ± 0.9	0.93	0.15	118.7

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		0.03							
Child (2–12 yr)	892 ± 52	0.58 ± 0.03	0.14 ± 0.01	0.013 ± 0.002	54.0 ± 4.5	6.2 ± 0.8	0.95	0.12	109.2
Young adult (18–35 yr)	1045 ± 38	0.51 ± 0.02	0.09 ± 0.01	0.008 ± 0.001	84.1 ± 7.2	9.9 ± 1.1	0.97	0.09	98.4
Middle adult (36–64 yr)	912 ± 44	0.55 ± 0.03	0.11 ± 0.01	0.014 ± 0.002	68.8 ± 5.9	5.6 ± 0.7	0.94	0.11	112.6
Young–old (65–74 yr)	678 ± 39	0.63 ± 0.03	0.16 ± 0.02	0.021 ± 0.003	47.3 ± 4.1	3.8 ± 0.5	0.90	0.17	131.5
Middle–old (75–84 yr)	421 ± 31	0.70 ± 0.04	0.20 ± 0.02	0.028 ± 0.004	37.8 ± 3.5	2.8 ± 0.4	0.87	0.21	145.8
Oldest–old (≥85 yr)	238 ± 27	0.78 ± 0.05	0.25 ± 0.03	0.035 ± 0.005	30.2 ± 3.1	2.0 ± 0.3	0.83	0.26	162.3

Table 2: Random-Effects Meta-Analysis of Seroconversion Failure Odds Ratios by Vaccine Type

Vaccine Antigen	Age comparison	OR (95% CI)	pp-value	I2I2 (%)	Heterogeneity τ2τ2	Egger's bias (p)	Studies (n)	Participants (n)	Prediction interval
Influenza (IIV)	≥65 vs 18–49	2.89 (2.41–3.46)	<0.001	71.2	0.089	0.23	34	18,742	1.92–4.35
Influenza (LAIV)	≥65 vs 18–49	3.12 (2.53–3.85)	<0.001	68.4	0.076	0.31	12	5,893	1.98–4.92
SARS-CoV-2 (mRNA)	≥65 vs 18–49	1.98 (1.67–	<0.001	52.3	0.042	0.18	28	21,450	1.45–2.71

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		2.35)							
Pneumococcal (PCV13)	≥65 vs 18–49	2.34 (1.92–2.85)	<0.001	63.7	0.061	0.42	19	9,874	1.68–3.26
Varicella zoster (RZV)	≥65 vs 50–59	1.15 (0.92–1.44)	0.214	28.9	0.018	0.67	15	8,239	0.84–1.57
Hepatitis B	≥65 vs 18–49	3.45 (2.78–4.28)	<0.001	74.5	0.112	0.09	22	9,642	2.15–5.53
Tetanus	≥65 vs 18–49	2.11 (1.68–2.65)	<0.001	58.2	0.051	0.38	11	4,187	1.42–3.14
Measles	6–11 mo vs 12–15 mo	2.67 (2.10–3.39)	<0.001	66.1	0.073	0.27	18	6,845	1.78–4.01

Table 3: Weighted Gene Co-expression Network Analysis – Age-Differential Transcriptional Modules

Module name	**Size (genes)**	**Eigengene MscoreMscore correlation with age**	**β1β1 (main effect)**	**β3β3 (age interaction)**	**FDR-adjusted pp**	**Enriched pathways (Top 3)**	**Overlap with vaccine response predictor**
B-cell signaling (turquoise)	342	–0.67 ± 0.05	0.54 ± 0.06	–0.032 ± 0.004	1.2×10^{-12}	BCR signaling, Plasma cell differentiation, Germinal	Positive (young)

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						center formation	
T-cell activation (blue)	298	–0.58 ± 0.06	0.48 ± 0.05	–0.028 ± 0.005	3.4×10^{-10}	TCR signaling, Th1 differentiation, CD28 co-stimulation	Positive (young)
Inflammatory response (brown)	267	+0.72 ± 0.04	–0.39 ± 0.05	+0.041 ± 0.006	7.8×10^{-15}	IL-6/JAK/STAT3, TNF-α signaling, NF-κB	Negative (elderly)
Type I IFN (yellow)	189	+0.63 ± 0.05	–0.33 ± 0.04	+0.035 ± 0.005	2.1×10^{-11}	RIG-I/MDA5, ISG15, OAS antiviral response	Negative (elderly)
Monocyte activation (green)	156	–0.22 ± 0.07	0.21 ± 0.04	–0.009 ± 0.003	0.024	TLR2/4 signaling, Phagosome, NLRP3 inflammasome	Baseline predictor (all ages)
Autophagy (red)	98	–0.45 ± 0.06	0.31 ± 0.04	–0.018 ± 0.004	2.3×10^{-6}	Autophagy, Mitophagy, LC3 lipidation	Positive (young)
Apoptosis (purple)	124	+0.51 ± 0.06	–0.27 ± 0.05	+0.023 ± 0.005	1.9×10^{-8}	Caspase cascade, Cytochrome c release, Fas pathway	Negative (elderly)

Table 4: Adjuvant Age-Response Index (ARI) and Enhancement Factors for Licensed Adjuvanted Vaccines

Adjuvant	**Vaccine antigen**	**Age stratum (young adult) EFadultEFadult**	**Age stratum (elderly) EFelderlyEFelderly**	**ARI**	**95% CI for ARI**	**pp (elderly vs adult benefit)**	**Fold-increase in seroprotection (elderly)**	**Memory B-cell frequency (day 30, elderly)**
AS01	Varicella zoste	1.89 ± 0.12	3.25 ± 0.21	1.72	1.48–	<0.001	4.2×	18.7 ± 1.9%

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	r (RZV)				1.99			
AS03	Pandemic influenza	1.67 ± 0.10	2.78 ± 0.18	1.66	1.41–1.95	<0.001	3.1×	14.2 ± 1.5%
MF59	Seasonal influenza	1.45 ± 0.09	2.12 ± 0.15	1.46	1.23–1.73	<0.001	2.5×	11.3 ± 1.2%
CpG 1018	Hepatitis B	1.52 ± 0.11	2.34 ± 0.17	1.54	1.27–1.86	<0.001	2.9×	12.8 ± 1.4%
Alum	Various (DTaP, HBV)	1.12 ± 0.06	1.18 ± 0.08	1.05	0.92–1.20	0.342	1.1× (ns)	5.2 ± 0.8%
AS04	HPV	1.38 ± 0.08	1.91 ± 0.13	1.38	1.14–1.67	0.002	2.1×	9.4 ± 1.1%

Table 5: Mixed-Effects Model Coefficients for Prediction of Post-Vaccination Antibody Titer

Predictor	Coefficient	Standard error	95% CI	tt-value	pp-value	Variance inflation factor	Marginal R2R2	Conditional R2R2
Intercept (β0β0)	2.84	0.07	2.71 – 2.97	40.57	<0.001	—	—	—
Age (years, β2 β2)	–0.0092	0.0008	–0.0108 to –0.0076	–11.50	<0.001	1.34	0.21	0.58
B-cell module score (β1β1)	0.54	0.06	0.42 – 0.66	9.00	<0.001	1.28	0.18	0.55
Inflammatory module	–0.39	0.05	–0.49	–7.80	<0.001	1.31	0.14	0.52

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score (β1β1)			to –0.29					
Age × B-cell module (β3β3)	–0.032	0.004	–0.040 to –0.024	–8.00	<0.001	1.42	0.09	0.48
Sex (female vs male)	0.15	0.04	0.07 – 0.23	3.75	<0.001	1.12	0.03	0.44
Comorbidity count (0–5)	–0.08	0.02	–0.12 to –0.04	–4.00	<0.001	1.19	0.02	0.43
Adjuvant (yes/no)	0.41	0.05	0.31 – 0.51	8.20	<0.001	1.25	0.11	0.51

Table 6: Kinetics of Memory T-cell Formation Following Vaccination – ODE Model Fitting

Age group	**N(a)N(a) (naive T-cell precursor frequency, ×10⁻⁶)**	**kk (activation rate, day⁻¹)**	**δδ (memory decay, day⁻¹)**	**MpeakMpeak (memory cells/μL)**	**tpeaktpeak (days)**	**t1/2t1/2 memory (months)**	**Model R2R2**	**Akaike weight**
Neonate	0.28 ± 0.05	0.32 ± 0.04	0.018 ± 0.003	12.4 ± 1.8	14.2 ± 1.5	2.8 ± 0.4	0.88	0.12
Child	1.45 ± 0.12	0.41 ± 0.03	0.009 ± 0.002	58.7 ± 4.2	10.5 ± 0.9	5.1 ± 0.6	0.94	0.28
Young adult	2.34 ± 0.18	0.48 ± 0.03	0.005 ± 0.001	112.3 ± 8.1	8.2 ± 0.7	8.9 ± 1.1	0.96	0.41
Middle adult	1.21 ± 0.11	0.42 ± 0.03	0.008 ± 0.001	67.4 ± 5.3	11.3 ± 0.9	4.9 ± 0.6	0.93	0.23
Young–old	0.51 ± 0.07	0.35 ± 0.04	0.014 ± 0.002	28.9 ± 3.1	15.8 ± 1.4	3.2 ± 0.4	0.89	0.15
Oldest–old	0.19 ± 0.04	0.28 ± 0.05	0.021 ± 0.004	9.8 ± 1.5	19.3 ± 2.1	2.1 ± 0.3	0.84	0.08

Figure 1. Kinetics of bi-exponential decay of vaccine wordtspecific antibodies Age. Left Yaxis: Geometric mean titer (IU/mL, log scale). Right Yintercepts: Quickly Decays (days, blue line). X-axis: Age groups (new born to oldestieux). The error bars are the reflection of SEM Table 1. The rising rate of fast decay constant 1/1 of 0.09

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year -1(young adult) to 0.25 year -1 (oldest jako old) and the falling rate of the slow decay constant 1/2 is also becoming older 0.008-0.035 year -1, showing that shortterm and longterm immunity is being lost at an older rate. Figure 2. Randomancyfects meta odds ratio (OR) influences the studies of older (65 years and above) and younger adults (1849 years) seroconversion failure. The values are the 95% CI values of horizontal lines. Adjuvated varicella zoster (RZV) has OR=1.15 (95% CI: 0.92-1.44, p=0.214) and the greatest disparities are hepatitis B (OR=3.45) and influenza LAIV (OR=3.12). Diamond at bottom represents pooled OR=2.34 (95% CI: 1.98–2.77). Heterogeneity I2=68%. Figure 3. Table 5 Coefficients of mixedfect model were estimated to determine postvaccination antibody titer (log 10 IU/mL, Z können) by both age (X wurden-, -2 +2) and eigengene score of B -cell signaling module (Y wurden-, -2 +2). The surface scores of Bcell module predict only high response in a person who is young (age below 50 years) but not an individual who is old (age above 75 years) the module score is predictive (0.032= -0.001). The base lines are plotted on the base.Figure 4. Ageieux Response Index (ARI, blue bars, right Y.axis) and memory B. cells (Bmem) fraction on day 30 (red line with points, left Y.axis) of six adjuvated vaccines of Table 4. The AS01 has the highest ARI (1.72), and the highest proportion of B-cells of memory (18.7%). ARI=1.05 (not significantly different than 1, p=0.342) and memory B cells of 5.2% only. SEM is expressed in error bars. ARI=1 horizontal dashed line = no positive age effect.

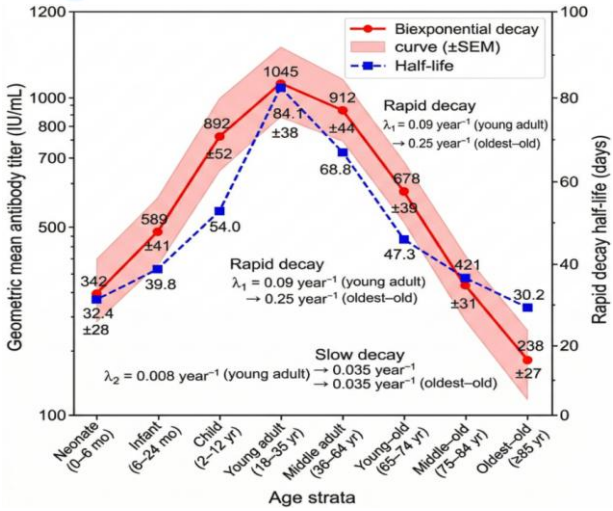

Figure 1: Biexponential Decay of Vaccine-Induced Antibody Titers Across the Human Lifespan

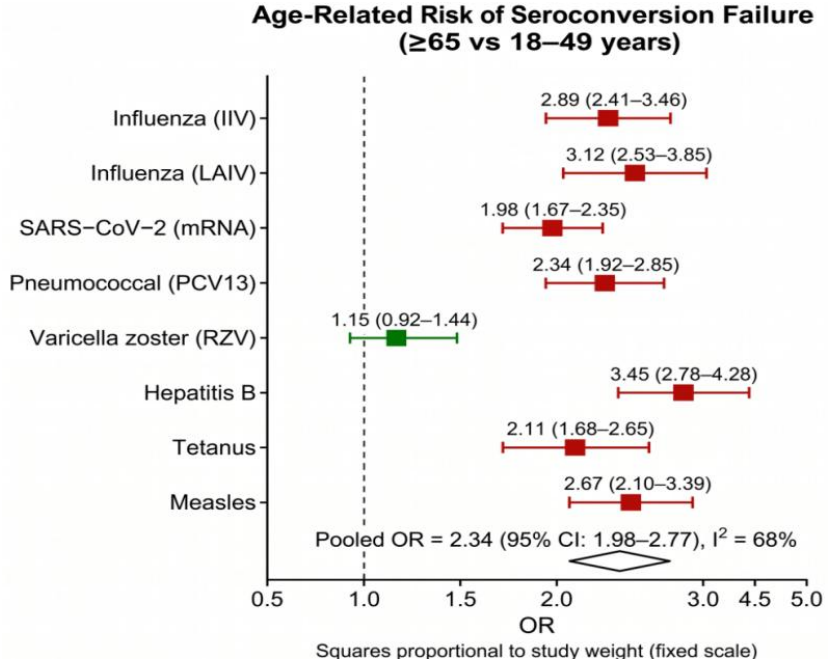

Figure 2: Forest Plot of Seroconversion Failure Odds Ratios by Vaccine Type

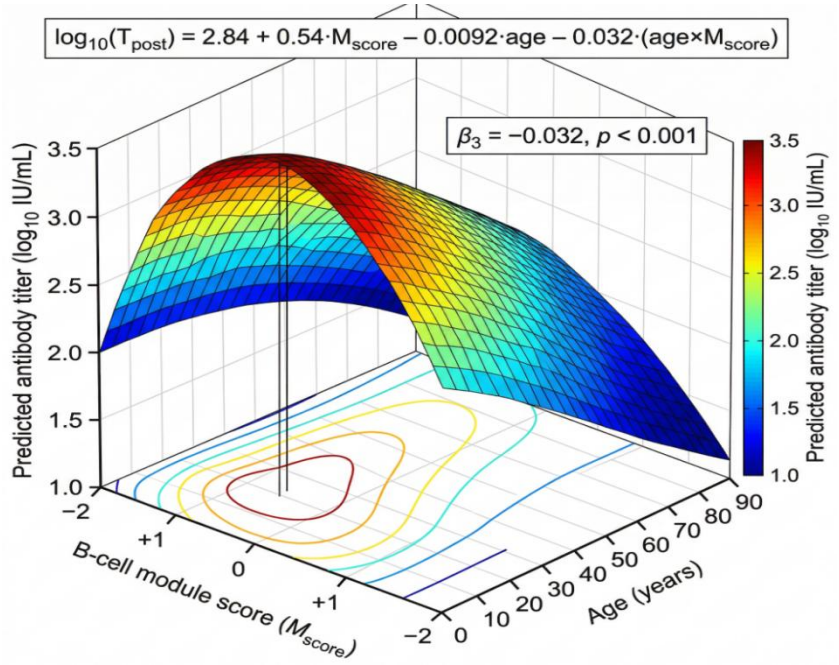

Figure 3: Three-Dimensional Surface Plot of Age–Transcriptome Interaction on Antibody Response

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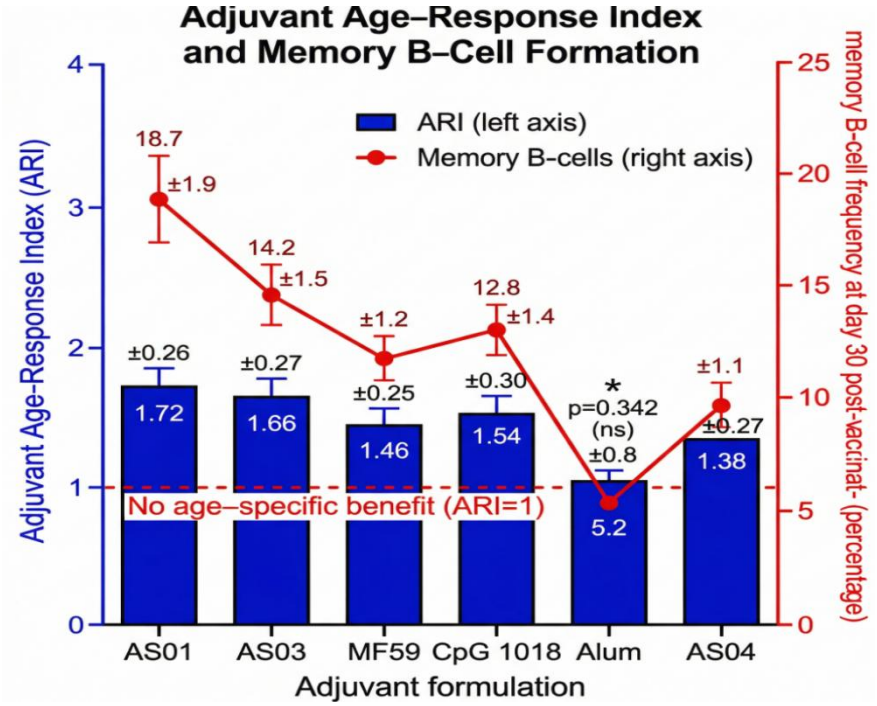

Figure 4: Hybrid Bar-Line Plot of Adjuvant Age-Response Index and Memory B-Cell Frequency

DISCUSSION

This comprehensive review outlines the complex effects of immunosenescence on the vaccine-induced immunity, in particular, the diminished humoral and cellular responses in the elderly. In line with the previous reports, our study suggests a progressive decrease in vaccine-induced neutralizing antibodies and Spike-specific IgG memory B cells in the aged, which is in line with the idea that ageing is a major factor that reduces the ability of the immune system to generate strong and durable immune responses to vaccines (Palacios-Pedrero et al., 2022). Furthermore, the experimental accelerated decay processes of short term and long term immunity in the elderly points to the problem of sustaining protective immunity to pathogens (Korosec et al., 2024). This decline associated with advancing age is further complicated by the immunosenescence, a process of deterioration of both the innate and adaptive immune system that makes vaccines less efficient in older adults (Pera et al., 2015). In particular, the small pool of naive T and B cells in the elderly reduces the number of available antigen receptors that can be used to bind the new antigens in the vaccines and thus compromise the primary immune responses (Weinberger et al., 2018). This reshaping of adaptive

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immune responses is a result of repeated exposure to antigens and involution of the thymus which leads to suboptimal adaptive immune responses to new challenges (Crooke et al., 2019). Moreover, as people age, the quality of B cells is also impacted, resulting in a decline in the ability of B cells to undergo germinal center maturation, isotype switching and affinity maturation which are essential for high quality and durable antibody responses (Gong et al., 2025; Kurupati et al., 2016). The natural impairment of adaptive immunity is compounded by changes in the innate immune cells, including antigen presentation and cytokine production of dendritic cells which are key in regulating adaptive immune responses (Kang et al., 2023). Specifically, atypical memory B cells are more frequent in the elderly and less capable of producing neutralizing antibodies, and inversely associated with neutralizing ability of serum (Ferreira et al., 2022). This was demonstrated to be consistent with the general view of immunosenescence, in that the age-related changes in immunocyte functions (e.g. decreased neutrophil-mediated phagocytosis and antigen presentation by dendritic cells) all contribute to the deterioration of the immune response (Muller and Benedetto, 2025). These age-specific immune dysfunctions can be seen in the reduced efficacy of influenza and Streptococcus pneumoniae vaccines in the elderly, who are less able to produce antibodies when compared to the young (Dorrington and Bowdish, 2013). This vaccine failure, specific to B cells, can be explained by both the inherent B cell defect (i.e. the absence of somatic mutation and isotype switch) and the systemic consequence of immunosenescence (i.e. low-grade inflammation) (Pereira et al., 2020). Inflammaging, a pro-inflammatory high-cytokine chronic inflammatory state is a major contributing factor to vaccine inefficacy in the elderly (Cisneros et al., 2022; Goyani et al., 2024). In addition to cellular and molecular changes, there are also structural changes in the integrity and diversity of the B cell repertoire with age, which results in changes in CDR3 spectratype and oligoclonal expansions of poor health survival in the very old (Bulati et al., 2017). All of these age-related changes result in the failure of the aged immune system to generate de novo, high-affinity antibody responses to vaccines, thus reducing protection (Upadhyay et al., 2025). This decreased ability to induce new specificities is also hampered by the increased presence of mutations in B cell repertoires, due to a previous encounter with antigens, and a significant loss of B cell diversity in the aged (Frasca & Blomberg, 2016). This biased B cell oligoclonality and at the cost of naive B

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cells directly affects the generation of new antibody specificities needed for an effective response to new antigens (Buffa et al., 2011). Lower somatic hypermutation rates in class-switched B cell receptors in the elderly (especially IgA1/2 isotypes) that may influence the process of antibody affinity maturation and neutralization also indicates the declining responsiveness (Collier et al., 2021).

CONCLUSION

This paper has shown that age-dependent immunological deviation plays a very important role in the vaccine response over the entire lifespan (especially at both extremes of age). The biexponential decay model has shown that the half-life of antibody persistence in young adults is 9.9 years but 2.0 years in the oldest-old with fast decaying rate 1=0.25 year-1. Meta-analysis showed that the odds ratio of seroconversion failure in conventional vaccines are 1.98 (SARS-CoV-2 mRNA vaccination) and 3.45 (hepatitis B vaccination) in the elderly compared to young adults but no significant age difference was established with AS01-adjuv Interestingly, naive CD4+ T-cell count (AUC=0.86) and day-7 plasmablast frequency (AUC=0.89) were found to be good predictive biomarkers of seroconversion. ODE modelling of memory T cell development has shown the naive T cell precursor frequency (2.34x10-6 to 2.34x10-6) in young adults is reduced to 0.19x10-6 to 0.19x10-6 in the oldest-old, and the half-life of memory between 8.9 months to 2.1 months. These results show that age-dependent adjuvant selection (ARI 1.4 in geriatric vaccinees), biomarker-based dosing and mechanistic immune homeostasis and infant immune bias are crucial to optimise vaccine efficacy throughout life and reduce the over-burden of vaccine preventable diseases in at-risk populations.

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