What time interval is needed between the administration of live attenuated vaccines?

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Clinical scenario

A mother consults you for her daughter's 12-month-old measles-mumps-rubella (MMR) vaccination. The girl's vaccination record reveals she had a Bacillus-Calmette-Guérin (BCG) vaccine two weeks prior because the family is planning to travel to India. You wonder what duration is needed between the administration of live attenuated vaccines to avoid diminishing vaccine responses.

Structured clinical question

What time interval is needed between the administration of live attenuated vaccines to avoid interfering with the immune response to either vaccine?

Search strategy and outcome

In February 2020, MEDLINE (1946 to present) was searched without any language limitations using the Ovid interface with the search terms detailed in the supplementary data.

Our search identified 4592 studies. Of these, 16 fulfilled the inclusion criteria of studies in humans investigating interference on immunogenicity of two or more live attenuated vaccines administered simultaneously or consecutively (Table 1; supplementary results and table 1). References were hand-searched for additional publications and no further relevant studies were found. One study was excluded because insufficient details were provided.¹

Commentary

Generally, simultaneous administration of vaccines on the same day is recommended to avoid missing opportunities for vaccination and to increase the probability that a child is fully vaccinated at the appropriate age.^{2,3} If two live vaccines cannot be given on the same day, many authorities recommend a minimum interval of four weeks between doses of live

attenuated vaccines.^{4, 5} This recommendation is based on three studies which were published over half a century ago.⁶⁻⁸ The first two studies showed that interferon levels were increased 6 to 11 days after measles vaccination and 4 to 7 days after yellow fever vaccine (YFV).^{6, 7} The third study showed that vesiculation and scab formation after smallpox vaccine were weaker when the vaccine was given between 4 and 20 days after measles vaccination.⁸ Because of these studies, it was hypothesised that the increased interferon observed after the first live attenuated vaccine might hamper the response to a second live attenuated vaccine if the second one is administered less than 28 days after the first. Additionally, there were two studies published in the early 1970s suggesting that simultaneous cholera (CV) and YFV causes diminished antibody responses to both vaccines.^{1, 9}

However, in our systematic review, we found limited evidence for the recommended minimum interval of four weeks between two live vaccines. Eight studies have investigated the effect of giving two live attenuated vaccines within 28 days of each other (Table 2).¹⁰⁻¹⁷ Three studies investigated the interaction between a measles-containing vaccine (MCV) and YFV,¹⁰⁻¹² three between oral rotavirus vaccine (ORV) and oral polio vaccine (OPV),¹⁵⁻¹⁷ one between measles vaccine and OPV,¹³ and one between CV and YFV.¹⁴ Only one study found lower antibody responses when two live attenuated vaccines were given within a time interval of 28 days (lower antibody responses to ORV when OPV was given 21 days after ORV compared with simultaneous administration).¹⁶

Most studies have focused on the effect of co-administering live attenuated vaccines rather than determining the minimum duration between vaccines necessary to avoid diminishing antibody responses. These studies have used a control group in which the vaccines have been separated by a duration of 4 or 6 weeks, on the assumption that this time interval is sufficiently long to preclude any interaction. From these studies, there is some evidence that

MMR and YFV should not be given on the same day, as this might decrease antibody responses to YF, mumps and rubella.^{10, 18} There is also some evidence that MMR and varicella (V) vaccines should not be given on the same day, as this might lower antibody responses to V (administered separately or in one vaccine).¹⁹⁻²¹ Although, there are no studies that measured antibody responses when MMR and V vaccines were given less than 28 days apart, retrospective cohort studies report that breakthrough disease is higher when the vaccines are given within this time interval.^{22, 23} YFV and CV given on the same day were associated with lower antibody responses to YFV but this interaction might only be transitory and further studies with longer follow-up are needed.⁹

For many combinations of currently used live attenuated vaccines (BCG, MMR, V, CV, ORV, live attenuated influenza vaccine (LAIV) and oral typhoid (OTV)), there have been no studies investigating the influence of one vaccine on the antibody response to another given within four weeks. Recent recommendations from the Public Health England state that these vaccines can be administered at any time before or after each other.²⁴ These recommendations also state that YFV can be given at any time in relationship to “most” live vaccines with the exception of MMR where these two vaccines should be given 28 days apart. This is based on the data detailed above suggesting sub-optimal antibody responses when these vaccines are given at the same time.¹⁸

Clinical bottom lines

- There is no evidence that live attenuated vaccines given within 28 days of each other diminish antibody responses, except for oral live attenuated vaccines (OPV and ORV) (Grade C).
- Giving some live attenuated vaccines (MMR and V, MMR and YFV, CV and YFV, OPV and ORV) on the same day might diminish antibody responses to one or both

vaccines, though the clinical relevance of this on protective efficacy is uncertain (Grade C).

- The pragmatic argument for ensuring vaccinations are not missed might outweigh the theoretical risk of interference in antibody response resulting from the administration of live vaccines simultaneously or within 28 days (Grade C).

Contributors

PZ did the search and prepared the manuscript and tables. AP and NC were involved in planning the study, interpreting results and multiple revisions of the manuscript. All authors gave approval for submission of this manuscript.

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Table 1 Findings of studies that have investigated the interference on vaccine immunogenicity of two or more different live attenuated vaccines administered consecutively

Citation	Age	Study type Level of evidence	Outcome	Key results of antibody responses (IgG unless otherwise stated) to live vaccines
Vaccines				
MMR vaccine and varicella (V) vaccine				
Englund <i>et al</i> ²⁵	15 to 24m	Single centre, double-blinded, placebo-controlled, randomised study (1b)	GMCs and SCRs 42d after vaccination	No differences for varicella, measles, mumps and rubella
USA	Group 1 (n=47): MMR +V			
1998	Group 2 (n=54): MMR + placebo; V 42d later			
Shinefield <i>et al</i> ¹⁹	12 to 23m	Single centre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs 42 and 365d after vaccination	V simultaneously with MMR • lower GMCs for varicella (10.5 vs 14.5 ELISA units, p-value ns) • lower SCRs for varicella (83 vs 91%, p-value ns)
USA	Group 1 (n=221): MMR + DTPa-Hib + V			
1998	Group 2 (n=223): MMR + DTPa-Hib; V 42d later			
White <i>et al</i> ²⁰	12 to 42m	Multicentre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs 42d after vaccination	MMRV • lower GMCs for varicella (6.9 vs 11.9 ELISA units, p<0.001) • lower SCRs for measles (96 vs 100%, p=0.03)
USA	Group 1 (n=160): MMRV + DTPa + OPV			
1997	Group 2 (n=158): MMR + DTPa + OPV; V 42d later			
Reuman <i>et al</i> ²¹	12 to 18m	Multicentre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs 42 and 365d after vaccination	MMRV • lower GMCs for varicella (8.3 vs 11.7 ELISA units, p=0.03) • higher GMCs for measles (126.5 vs 90.9 ELISA units, p=0.004)
USA	Group 1 (n=147): MMRV + Hib			
1997	Group 2 (n=147): MMR + Hib; V 42d later			
Measles-containing vaccine (MCV) and yellow fever vaccine (YFV)				
Goujon <i>et al</i> ¹⁰	6 to 24m	Multicentre, retrospective case-control study (3b)	GMCs and SCRs time ns	YFV simultaneously with MCV • lower SCRs for YF (92 vs 100%, p-value ns) GMCs against YF and MMR increased as the time between immunisation increased
France	Group 1 (n=62): MCV + YFV			
2017	Group 2 (n=50): MCV; YFV 1-27d later Group 3 (n=19): MCV; YFV >28d later			
Michel <i>et al</i> ¹¹	9 to 14m	Multicentre, prospective observational study (4)	GMCs and SCRs 28 to 60d after vaccination	No differences for YF
Senegal	Group 1 (n=49): YFV + MCV			
French Guiana	Group 2 (n=209): MCV; YFV 7-28d later			
2015				

Nascimento <i>et al</i> ⁸ Brazil 2011	12 to 23m Group 1 (n=839): YFV + MMR Group 2 (n=852): MMR; YFV >30d later	Multicentre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs 30d after vaccination	YFV simultaneously with MMR <ul style="list-style-type: none"> • lower GMCs against YF (1065 vs 3385 mIU/ml, p<0.001) • lower GMCs against rubella (25 vs 60 IU/ml, p<0.001) • lower SCRs for YF (70 vs 88%, p<0.001) • lower SCRs for rubella (90 vs 97%, p<0.001) • lower SCRs for mumps (61 vs 71%, p<0.001) <p>GMCs against YF and rubella increased as the time between immunisation increased</p>
Stefano <i>et al</i> ¹² Brazil 1999	9m Group 1 (n=57): MCV; YFV 1-6d later Group 2 (n=53): MCV; YFV 7-13d Group 3 (n=65): MCV; YFV 14-21d later Group 4 (n=54): MCV; YFV 22-27d later Group 5 (n=65): MCV; YFV >28d later	Multicentre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs >42d after vaccination	No differences for YF
Measles vaccine (MV) and oral polio vaccine (OPV)				
Pannuti <i>et al</i> ¹³ Brazil 1987	9m Group 1 (n=23): MV; OPV 2-6d later Group 2 (n=37): MV; OPV 9-13d later Group 3 (n=42): MV; OPV 16-20d later Group 4 (n=15): MV; OPV 23-26d later Group 5 (n=88): MV; OPV >28d later	Multicentre, prospective observational study (4)	SCRs 14-19d after vaccination for children with MV <28d after OPV and >20d after vaccination for children with MV >28d after OPV	No differences for measles
Oral polio vaccine (OPV) and oral rotavirus vaccine (ORV)				
Zaman <i>et al</i> ¹⁵ Bangladesh 2009	10w Group 1 (n=100): OPV + ORV (2 doses at an interval of 28d) Group 2 (n=100): OPV + DTPw-HepB, ORV 15d later (2 doses at an interval of 28d) Both groups received OPV + DTPw-HepB at 42d	Single centre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs (IgA) 30d after vaccination	OPV simultaneously with ORV <ul style="list-style-type: none"> • higher GMCs for polio type 2 (839 vs 455 U/ml)
Ciarlet <i>et al</i> ¹⁶ Mexico Costa Rica Guatemala Brazil 2008	6 to 12w Group 1 (n=368): ORV + OPV (3 doses 57-70d apart) Group 2 (n=326): ORV; OPV 14-28d later (3 doses 42d apart)	Multicentre, non-blinded, controlled, randomised study (1b)	GMCs and SCRs 42d after vaccination	OPV simultaneously with ORV <ul style="list-style-type: none"> • lower GMCs for IgA (155 vs 293 U/ml) and ORV neutralizing IgGs (G1 126 vs 183, P1A 85 vs 131) but not for others (G2 27 vs 30, G3 21 vs 23, G4 59 vs 75)

Jalil <i>et al</i> ¹⁷	6w	Single centre, prospective observational study (4)	SCRs 21d after ORV SPRs 42d after ORV	OPV simultaneously with ORV • higher SCRs for ORV (18 vs 9%)
Pakistan	Group 1 (n=25): ORV + OPV; OPV 42d and 84d later; DTP 15w later			
1991	Group 2 (n=24): ORV + DTP; OPV 21d later; OPV + DTP 42d and 84d later			
Cholera vaccine (CV) and Japanese encephalitis vaccine (JEV)				
Poveda <i>et al</i> ¹⁴	Adults, age ns	Single centre, retrospective, case-control study (3b)	GMCs and SCRs 47 ± 40m after JEV	No differences for YF
France	Group 1 (n=30): CV + JEV (			
1990	Group 2 (n=26): CV; JEV 1-10d later Group 3 (n=28): JEV; CV 1-10d later Group 4 (n=17): CV; JEV >10d later or JEV; CV >10d later Group 5 (n=20): JEV only			
Gateff <i>et al</i> ⁸	2 to 5y	Single centre, prospective, case-control study (3b)	GMCs and SCRs 30d after vaccination	CV simultaneously with JEV vs JEV alone • lower GMCs for JE (8.7 vs 16.7 units) • lower SCRs for JE (98.6 vs 70%)
Cameroun	Group 1 (n=60): CV + JEV Group 2 (n=95): CV; JEV 28d later Group 3 (n=69): CV (2 doses one week apart); JEV 28d later Group 4 (n=69): JEV; CV 28d later Group 5 (n=70): JEV only Group 6 (n=108): CV only			CV 28d before JEV vs JEV alone • lower GMCs for JE (13.2 vs 16.7 units) • lower SCRs for JE (98.6 vs 95%)
1973				CV 28d (2 doses with a one-week interval) before JEV vs JEV alone • lower GMCs for JE (11.7 vs 16.7 units) • lower SCRs for JE (98.6 vs 96.5%)
	2 to 5y		GMCs and SCRs 60d after vaccination	No differences for JE
	Group 1 (n=82): CV + JEV Group 2 (n=72): JEV only			
Japanese encephalitis vaccine (JEV) and yellow fever vaccine (YFV)				
Nasveld <i>et al</i> ²⁶	18 to 53y	Single centre, double-blinded, placebo-controlled randomised study (1b)	GMCs and SCRs 30d after JEV	YFV 30d after JEV vs JEV followed by YFV 30d later • higher GMCs for JE (1500 vs 400 units, p-value ns) • higher SCRs for JE (100 vs 91%, p-value ns)
Australia	Group 1 (n=18): JEV + YFV; placebo 30d later Group 1 (n=18): placebo; JEV + YFV 30 days later Group 2 (n=36): JEV; YFV 30d later Group 3 (n=36): YFV; JEV 30d later			YFV 30d after JEV vs JEV simultaneously with YFV • higher GMCs for JE (1500 vs 150 units, p-value ns) • higher SCRs for JE (100 vs 96%, p-value ns)
2010				
Monath <i>et al</i> ²⁷	18 to 58y	Single centre, double-blinded, controlled randomised study (1b)	SCRs 30d after vaccination	YFV 30d after JEV • lower SCRs for JE-CV (64 vs 91%, p-value ns)
USA	Group 1 (n=11): JEV; YFV 30d later Group 2 (n=11): YFV; JEV 30d later			
2003				

CV – cholera vaccine
d – days
DTPa-Hib – diphtheria-tetanus-acellular pertussis-*Haemophilus influenzae* type b
GMC – geometric mean antibody concentration
Hib – *Haemophilus influenzae* type b vaccine
Ig – immunoglobulin
JEV – Japanese encephalitis vaccine
m – months
MCV – measles-containing vaccine
MMR – measles-mumps-rubella vaccine
MMRV – measles-mumps-rubella-varicella vaccine
MV – measles vaccine
ns – not specified
OPV – oral polio vaccine
ORV – oral rotavirus vaccine
SCR – seroconversion rates
SPR – seroprotection rates
w – weeks
V – varicella
y – years
YFV – yellow fever vaccine

Table 2 Time intervals investigated between the administration of live attenuated vaccines

	BCG	MCV	Varicella	YFV	JEV	OPV	CV	OTV	ORV	LAIV
BCG		ns	ns	ns	ns	ns	ns	ns	ns	ns
MCV			42d	1-28d >28d	ns	2-26d >28d	ns	ns	ns	ns
Varicella				ns	ns	ns	ns	ns	ns	ns
YFV					30d	ns	1-10d >10d 28d	ns	ns	ns
JEV						ns	ns	ns	ns	ns
OPV							ns	ns	14-28d	ns
CV								ns	ns	ns
OTV									ns	ns
ORV										ns
LAIV										

BCG – Bacillus-Calmette-Guérin vaccine

CV – cholera vaccine

d – days

JEV – Japanese encephalitis vaccine

LAIV – live attenuated influenza

MCV – measles-containing vaccine

OPV – oral polio vaccine

ORV – oral rotavirus vaccine

OTV – oral typhoid vaccine

YFV – yellow fever vaccine