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Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials

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Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers

A pooled analysis of randomized trials

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[†]ActHIB is a registered trademark of Sanofi Pasteur SA; PedvaxHIB, M-M-R II, and Varivax are registered trademarks of Merck and Co., Inc.

Keywords: *Haemophilus influenzae* type b, *Neisseria meningitidis* serogroups C and Y, MMR, varicella, vaccination, toddlers

A pooled analysis was conducted of 1,257 toddlers who received a fourth dose of *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine (HibMenCY-TT) or Hib conjugate vaccine (Hib polysaccharide conjugated to *N. meningitidis* outer membrane protein) coadministered with measles-mumps-rubella (MMR) and varicella (VAR) vaccines (NCT00134719/NCT00289783). Noninferiority of immunological responses to MMR and VAR was demonstrated between groups and incidences of MMR- and VAR-specific solicited symptoms were similar, indicating that HibMenCY-TT can be coadministered with MMR and VAR.

Introduction

Previous studies showed that a novel, combined *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroups C and Y conjugate vaccine that uses tetanus toxoid as carrier protein (HibMenCY-TT) was immunogenic with an acceptable safety profile when administered to infants as a 3-dose primary series,¹⁻⁵ with a fourth dose in the second year of life.^{2,4-6}

The vaccination schedule for HibMenCY-TT is consistent with the current Hib immunization schedule recommended by the United States (US) Advisory Committee on Immunization Practices, which includes a fourth dose of Hib at 12 to 15 mo of age.⁷ In Australia, a fourth dose of Hib conjugate vaccine is routinely given at 1 y of age. According to these schedules, HibMenCY-TT could potentially be coadministered with the combined measles,

mumps and rubella vaccine (MMR) and monovalent varicella vaccine (VAR). To facilitate integration of HibMenCY-TT into toddler vaccination schedules, it is important to demonstrate a lack of immune interference and an acceptable safety profile when MMR, VAR and HibMenCY-TT are given at the same time.

In 2 randomized controlled studies,^{4,5} infants received either HibMenCY-TT or Hib polysaccharide conjugated to tetanus toxoid (Hib-TT; *ActHIB*[®], Sanofi Pasteur SA, Lyon, France) at 2, 4 and 6 mo of age, followed at 12 to 15 mo of age by 1 dose of HibMenCY-TT or Hib polysaccharide conjugated to *N. meningitidis* outer membrane protein (Hib-OMP; *PedvaxHIB*[®], Merck and Co., Inc. Whitehouse Station, NJ USA) coadministered with MMR (*M-M-R*[®] II; Merck and Co., Inc.) and VAR (*Varivax*[®]; Merck and Co., Inc.). Hib-OMP was used for the toddler dose at the request of the US Food and Drug Administration, because

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Table 1. Number of subjects in relevant study cohorts

Group	Total	Australian study		US immunogenicity cohort ^a		Pooled	
		HibMenCY-TT	Hib-OMP	HibMenCY-TT	Hib-OMP	HibMenCY-TT	Hib-OMP
Enrolled in the fourth dose phase	1648	626	206	618	198	1244	404
Fourth dose total vaccinated cohort	1645	625	204	618	198	1243	402
Reasons for exclusion from ATP cohort:							
Administration of forbidden vaccine		0	0	4	0	4	0
Study vaccine dose administered contrary to protocol		11	2	54	13	65	15
Ineligibility for persistence analysis ^b		0	0	46	8	46	8
Essential safety data missing		11	4	0	0	11	4
Inappropriate age at fourth dose		3	0	1	0	4	0
Administration of forbidden medication		0	0	1	0	1	0
Infection related to vaccine ^c		0	0	1	0	1	0
Noncompliance with blood sampling schedule		28	5	49	23	77	28
Essential serological data missing		17	11	72	22	89	33
Data error ^d		1	0	1	0	2	0
Fourth dose ATP cohort for immunogenicity	1257	554	182	389	132	943	314

^aFor the US cohort, pneumococcal conjugate vaccine (*Prevnar*[™], Pfizer Inc.) was a concomitant vaccine, in accordance with local recommendations.

^bSubjects excluded from according-to-protocol cohort for immunogenicity (primary phase) unless reason for exclusion was noncompliance with protocol-defined serum sampling windows or lack of availability of immunogenicity results at post-dose 3 time point. ^cOne subject in the HibMenCY-TT group developed varicella infection before administration of varicella vaccine. ^dObvious incoherence between pre- and post-fourth dose vaccination data. Note: the number of subjects excluded for a specific reason does not take into account subjects already excluded because of reasons presented previously.

US prescribing information for Hib-TT does not include immunogenicity data for children aged between 12 and 15 mo.⁸ The Hib, MenC and MenY immunogenicity results from both studies were reported previously in reference 4 and 5.

The designs of the studies were sufficiently similar to allow a pooled analysis of immune responses to the coadministered MMR and VAR in the HibMenCY-TT group relative to those in the Hib-OMP control group at 12 to 15 mo of age.

Results

There were 1,648 subjects in the pooled data set (Table 1); 1,645 comprised the TVC (3 subjects were enrolled but did not receive study vaccines) and 1,257 comprised the ATP cohort for immunogenicity. The demographic characteristics of the groups (TVC) were comparable in both countries. Mean age (\pm standard deviation) in the Australian study was 12.0 \pm 0.3 and 12.0 \pm 0.2 mo in the HibMenCY-TT and Hib-OMP groups, respectively, and 12.1 \pm 0.5 and 12.3 \pm 0.6 mo in the US HibMenCY-TT and Hib-OMP groups, respectively. In the Australian study, 49% of the HibMenCY-TT group and 47% of the Hib-OMP group were female; in the US cohort, 47% and 48%, respectively, were female. At least 94% in both Australian groups were white/Caucasian; 77–82% were white/Caucasian in both US groups, and 7% and 11% were African-American in the US HibMenCY-TT and Hib-OMP groups, respectively.

Conditions to pool the data were met (Fig. 1), with seroconversion rates to measles, mumps, and varicella and the seroresponse

rate to rubella in both the HibMenCY-TT and Hib-OMP groups of both studies exceeding 93% 42 d after the fourth dose (Table 2). The pooled data indicated that seroconversion or seroresponse levels in both groups were at least 95% for measles and at least 99% for mumps, rubella and varicella, with antibody geometric mean concentrations/titers within the same range in both groups (Table 2). Statistical noninferiority of responses to MMR and VAR was demonstrated (Fig. 1).

There were no statistically significant differences between the HibMenCY-TT group and Hib-OMP group with respect to solicited symptoms specific to the coadministered MMR and VAR ($p \geq 0.05$ for all relative risks) (Table 3). The most frequently reported solicited symptom during the 43-d period following administration of MMR and VAR was fever $\geq 38^\circ\text{C}$ (45.8% and 48.7% of subjects in the HibMenCY-TT and Hib-OMP groups, respectively), with a peak in incidence at around day 9 in both groups (data not shown). Fever $> 40.0^\circ\text{C}$ was infrequent ($< 2\%$ in both groups). There were no reports of meningeal signs or febrile convulsions in the 43-d post-vaccination period. Parotid/salivary gland swelling was reported in 4 subjects in the HibMenCY-TT group (0.3%), with no reports in the Hib-OMP group; all reports were from Australia and all were considered by the investigator as related to vaccination. Two were categorized as grade 3, defined as swelling with accompanying general symptoms, occurred 12 to 14 and 14 to 17 d after vaccine administration, and were medically reviewed as a requirement of the study. All parotid/salivary gland swelling episodes resolved without sequelae. Rashes were reported

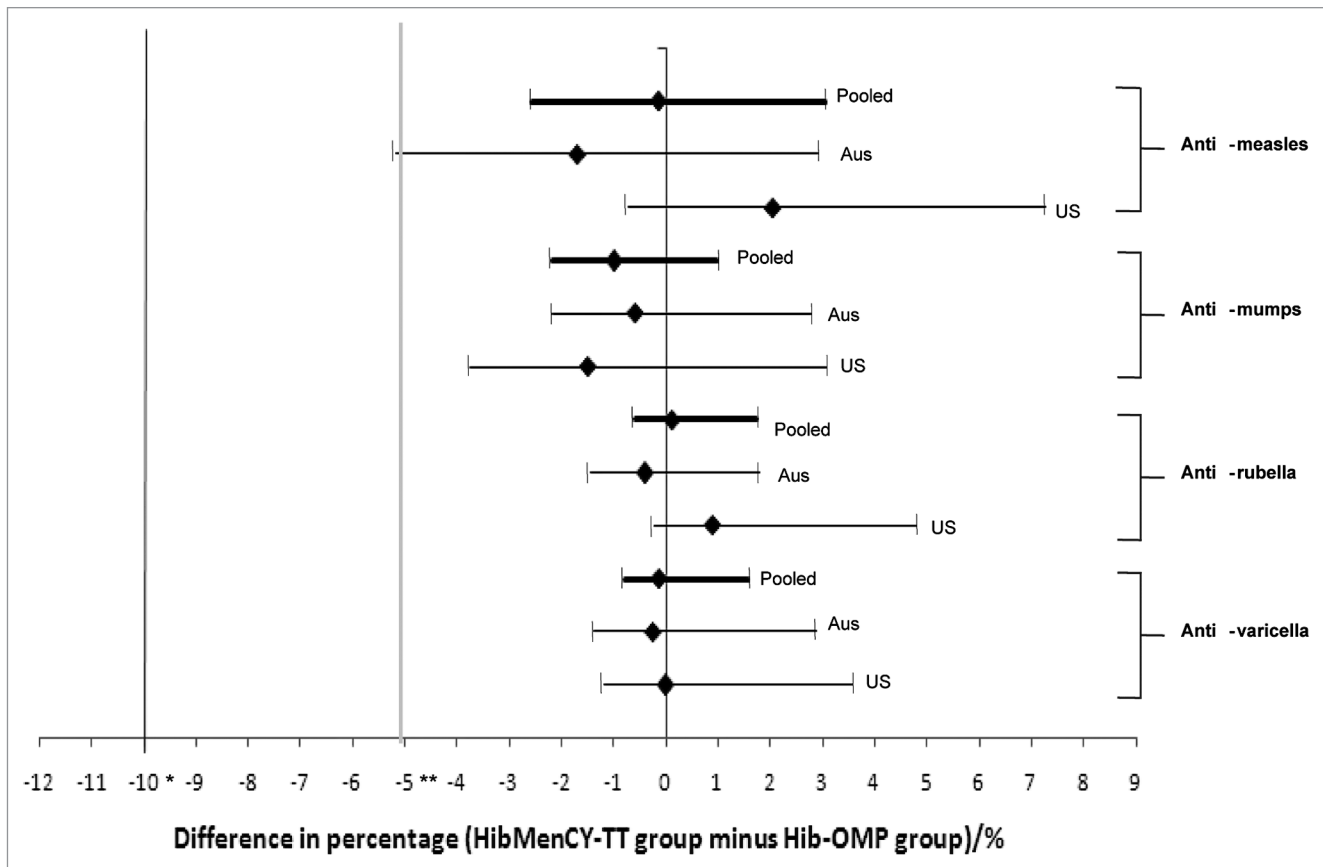


Figure 1. Difference between the HibMenCY-TT and Hib-OMP groups in percentage of subjects who seroconverted for measles, mumps and varicella and with a seroresponse to rubella 42 d post-fourth dose of HibMenCY-TT/Hib-OMP in the Australian study (Aus), US immunogenicity cohort (US), and pooled analysis (Pooled) (ATP cohorts for immunogenicity; subjects who were seronegative at baseline). Limits represent 95% confidence intervals. Footnote: Anti-measles seroconversion: post-vaccination antibody concentration ≥ 150 mIU/mL in initially seronegative subjects (< 150 mIU/mL); anti-mumps seroconversion: post-vaccination antibody titer ≥ 28 ED₅₀ in initially seronegative subjects (< 28 ED₅₀); anti-rubella seroresponse: post-vaccination antibody concentration ≥ 10 IU/mL in initially seronegative subjects (< 4 IU/mL); anti-varicella seroconversion: post-vaccination antibody titer $\geq 1:5$ in initially seronegative subjects ($< 1:5$); *limit of non-inferiority varicella; **limit of non-inferiority measles, mumps and rubella.

in 25.0% and 22.6% of subjects in the HibMenCY-TT and Hib-OMP groups, respectively.

Discussion

In 2 randomized controlled studies, 3 doses of HibMenCY-TT in infancy followed by 1 dose at 12 to 15 mo of age induced robust anti-Hib and anti-meningococcal serogroups C and Y immune responses and had an acceptable safety profile.^{4,5} Here, pooled analysis of data from these studies demonstrated noninferiority of immunological responses to MMR and VAR when concomitantly administered with the fourth dose of HibMenCY-TT compared with coadministration with a fourth dose of monovalent Hib-OMP. Previous analyses showed the percentages of children with anti-polyribosylribitol phosphate (PRP) antibody concentration ≥ 1.0 $\mu\text{g}/\text{mL}$ were high after the fourth HibMenCY-TT dose and consistent with the Hib-OMP control group, and that anti-PRP geometric mean concentrations were significantly higher than in Hib-OMP recipients.^{4,5} These results were in line with a study of HibMenCY-TT vs. monovalent Hib-TT vaccine in which MMR and VAR were not coadministered with the fourth dose.⁶ This

suggests immune responses to HibMenCY-TT, MMR and VAR are not compromised when administered together, although the possibility of interference cannot be completely excluded because no group in the current study received a fourth dose without MMR or VAR, or received MMR and VAR alone.

The reactogenicity profile of MMR and VAR was comparable when coadministered with HibMenCY-TT or Hib-OMP, as indicated by similar incidences of MMR- and VAR-specific solicited symptoms in both groups. Also, the incidence of fever $>38.5^\circ\text{C}$ in the HibMenCY-TT and Hib-OMP groups was consistent with the incidence of fever $\geq 38.9^\circ\text{C}$ reported in a study in which a group of children aged 12 to 23 mo received MMR and VAR alone.⁹ Parotid/salivary gland swelling was reported in less than 1% of subjects in the HibMenCY-TT group, which was consistent with a review of various randomized studies involving 3 different MMR vaccines that also showed low incidence of this adverse event ($\leq 1.8\%$).¹⁰

The studies included in this pooled immunogenicity analyses had several limitations. Approximately one-third of enrolled infants in the US immunogenicity cohort were excluded from

Table 2. Proportion of subjects who seroconverted to measles, mumps, or saricella or achieved a seroresponse to rubella 42 d post-fourth dose in the Australian, United States and pooled study groups (according-to-protocol cohort for immunogenicity; subjects who were seronegative at baseline)

Antibody (Cut-off)	Australia				United States				Pooled					
	HibMenCY-TT Group		Hib-OMP Group		HibMenCY-TT Group		Hib-OMP Group		HibMenCY-TT Group		Hib-OMP Group			
	N	Rate (%)	N	Rate (%)	N	Rate (%)	N	Rate (%)	N	Rate (%)	GMC (µg/mL) or GMT	N	Rate (%)	GMC (µg/mL) or GMT
Measles (≥150 mIU/mL)	501	93.6 (91.1, 95.6)	171	95.3 (91.0, 98.0)	351	98.6 (96.7, 99.5)	115	96.5 (91.3, 99.0)	852	95.7 (94.1, 96.9)	1990.0 (1852.2, 2138.0)	286	95.8 (92.8, 97.8)	1989.5 (1765.4, 2242.2)
Mumps (≥28 ED₅₀)	332	99.4 (97.8, 99.9)	110	100 (96.7, 100)	269	98.5 (96.2, 99.6)	81	100 (95.5, 100)	601	99.0 (97.8, 99.6)	124.4 (117.7, 131.4)	191	100 (98.1, 100)	115.9 (105.5, 127.3)
Rubella (≥10 IU/mL)	500	99.6 (98.6, 100)	171	100 (97.9, 100)	350	100 (99.0, 100)	113	99.1 (95.2, 100)	850	99.8 (99.2, 100)	81.4 (77.5, 85.4)	285	99.6 (98.1, 100)	74.9 (68.9, 81.4)
Varicella (≥1:5)	404	99.8 (98.6, 100)	119	100 (96.9, 100)	319	100 (98.9, 100)	104	100 (96.5, 100)	723	99.9 (99.2, 100)	407.1 (389.4, 425.5)	223	100 (98.4, 100)	394.1 (364.6, 426.0)

N indicates number of subjects with available serology results; rate, seroconversion or seroresponse rate (95% confidence interval); GMC/GMT, geometric mean concentration/titer; anti-measles seroconversion, post-vaccination antibody concentration ≥ 150 mIU/mL in initially seronegative subjects (< 150 mIU/mL); anti-mumps seroconversion, post-vaccination antibody titer ≥ 28 ED₅₀ in initially seronegative subjects (< 28 ED₅₀); anti-rubella seroconversion, post-vaccination antibody concentration ≥ 10 IU/mL in initially seronegative subjects (< 4 IU/mL); anti-varicella seroconversion, post-vaccination antibody titer ≥ 1:5 in initially seronegative subjects (<1:5).

Table 3. Pooled results. Incidence of solicited general adverse events specific to coadministered measles-mumps-rubella and varicella vaccines reported within the 43-d post-vaccination period following the fourth dose (total vaccinated cohort).

Symptom	Severity	HibMenCY-TT group			Hib-OMP group			Relative risk ^a (95% CI)	p-value
		N	n	%	N	n	%		
Meningeal signs/ febrile convulsion	All	1163	0	0	374	0	0	NC	NC
	Grade 3	1163	0	0	374	0	0	NC	NC
Parotid/salivary gland swelling	All	1163	4	0.3	374	0	0	INF (0.21, INF)	0.653
	Grade 3	1163	2	0.2	374	0	0	INF (0.06, INF)	1.000
Fever	All	1167	535	45.8	374	182	48.7	0.94 (0.80, 1.12)	0.522
	> 38.5°C	1167	339	29.0	374	114	30.5	0.95 (0.77, 1.19)	0.700
	> 39.0°C	1167	191	16.4	374	58	15.5	1.06 (0.78, 1.44)	0.778
	> 39.5°C	1167	84	7.2	374	29	7.8	0.93 (0.60, 1.47)	0.806
	> 40.0°C	1167	20	1.7	374	7	1.9	0.92 (0.37, 2.57)	0.994
Rash	All	1166	291	25.0	376	85	22.6	1.11 (0.87, 1.42)	0.455
	Grade 3	1166	38	3.3	376	10	2.7	1.23 (0.60, 2.76)	0.702

^aHibMenCY-TT over Hib-OMP. N indicates number of subjects with the documented dose; n/%, number/percentage of subjects reporting a specified symptom; NC, not calculated because no events reported; INF, infinity. p-value, 2-sided Exact Stratified Test conditional to number of cases; fever, rectal or axillary/tympanic temperature ≥ 38.0°C. Grade 3: meningeal signs/febrile convulsion that prevented normal, everyday activities; parotid/salivary gland swelling, with accompanying general symptoms; temperature > 40.0°C; rash with 200 or more papules, vesicles and/or crusts.

the ATP cohort for immunogenicity because of noncompliance with the blood sampling schedule or insufficient blood samples. Additionally, the majority of subjects in both studies were white/Caucasian. Future studies should further explore immunogenicity in other racial groups. Other potential limitations were the lack of a control group that did not receive *M-M-R*[®] II and *Varivax*[®] without the co-administration of licensed Hib vaccine, and lack of blinding of study personnel to treatment group, which could have influenced the assessment of reactogenicity, although in this instance one might expect the bias to be against the investigational vaccine, which includes two additional antigens. Also,

the results of group comparisons should be interpreted with caution considering that there was no adjustment for multiplicity and the study was not powered for these comparisons, meaning that definite conclusions cannot be made regarding the relative risk of a given adverse event.

In conclusion, the results of this pooled analysis of data from 2 randomized controlled studies indicate that a dose of HibMenCY-TT at 12 to 15 mo of age, given as part of a 4-dose HibMenCY-TT series, can be administered with an acceptable safety profile without diminishing immune responses to MMR and VAR.

Materials and Methods

Immunogenicity data available from Australian children included in a phase II randomized controlled study⁴ (NCT00134719) and US children enrolled in a phase III randomized controlled study⁵ (NCT00289783) were assessed. The studies, which were described in detail previously in reference 4 and 5, were designed in a similar way within the context of each country's immunization schedule, with the pre-specified objective of pooling data for the primary objective of assessing the non-inferiority of MMR and VAR co-administered with Hib-MenCY compared with co-administration with a licensed Hib vaccine. Conditions to pool the data were therefore defined prospectively, and were determined on the grounds of comparable immunogenicity between studies and were met if the point estimates of the difference between the HibMenCY-TT and Hib-OMP groups were above the predefined noninferiority limits in each study in terms of anti-measles seroconversion, anti-mumps seroconversion, anti-rubella seroresponse and anti-varicella seroconversion.

Immunogenicity analyses were performed on the pooled according-to-protocol (ATP) cohorts for immunogenicity from each study, defined as vaccinated children who met all eligibility criteria, complied with protocol-defined procedures, and had antibody assay results available for at least 1 antigen component. Cut-offs for seropositivity were defined as follows: anti-measles, enzyme-linked immunosorbent assay (ELISA) value ≥ 150 mIU/mL; anti-mumps, neutralization test value ≥ 28 ED₅₀; anti-rubella, ELISA value ≥ 4 IU/mL; anti-varicella fluorescent antibody membrane assay value $\geq 1:5$. Seroconversion for antibodies to measles, mumps and varicella was defined as the presence of detectable levels of the relevant antibodies at 42 d post-vaccination in subjects who were seronegative before vaccination. Seroresponse for rubella was defined as the appearance of anti-rubella virus antibodies to a concentration ≥ 10 IU/mL in subjects who were seronegative before vaccination (concentration < 4 IU/mL).

The coprimary objectives of the pooled immunogenicity analysis were to demonstrate noninferiority of MMR and VAR when coadministered with a dose of HibMenCY-TT compared with MMR and VAR coadministered with a dose of Hib-OMP in terms of anti-measles seroconversion, anti-mumps seroconversion, anti-rubella seroresponse and anti-varicella seroconversion at 42 d (range 35–56 d) after administration of the vaccines. The pooling criterion prespecified in the study protocols stated that the data could be pooled if, in each individual study, the point estimate for the group difference in seroconversion/seroresponse rates (HibMenCY-TT group minus Hib-OMP group) was $\geq -5\%$ for measles, mumps and rubella, and $\geq -10\%$ for varicella (note: the individual studies were not adequately powered to demonstrate a lower limit higher than the noninferiority criterion). Assessment of noninferiority was based on standardized asymptotic 95% confidence intervals (CIs) for the difference between groups (HibMenCY-TT group minus Hib-OMP control group) in percentage of subjects reaching the separate pre-specified endpoints for each of the MMR and VAR components. Noninferiority would be demonstrated if the lower limit of the

95% CI was above -5% for measles, mumps and rubella, and above -10% for varicella.

Parents/guardians of subjects completed diary cards with any solicited symptoms specific to MMR and VAR vaccination: fever $\geq 38^\circ\text{C}$ measured by any route, rash/exanthem, parotid/salivary gland swelling, and any suspected meningeal signs or febrile convulsions over a 43-d follow-up period after vaccination. Subjects with symptoms of parotid swelling were to return to the study center to be medically examined to confirm the diagnosis of parotiditis. As planned in the study protocols, the reactogenicity and safety analysis of these symptoms was performed on subjects in the pooled total vaccinated cohorts (TVCs) from both studies with safety data available (i.e., diary cards returned). Relative risk (percentage of subjects reporting a specific symptom in HibMenCY-TT group over percentage in Hib-OMP group) was calculated with exact 95% CI for each symptom. p-values were calculated using a 2-sided Exact Stratified Test conditional to number of cases and taking into account the study effect.

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