Anhang

Symptom Impfung	Anzahl (%)	
	IC51 (n = 1993)	Placebo (n = 657)
Schmerz		
Erste Impfung	369 (18,5)	102 (15,5)
Zweite Impfung	210 (10,5)	62 (9,4)
Juckreiz		
Erste Impfung	15 (0,8)	11 (1,7)
Zweite Impfung	15 (0,8)	8 (1,2)
Druckdolenz		
Erste Impfung	414 (20,8)	114 (17,4)
Zweite Impfung	295 (14,8)	79 (12,0)
Verhärtung		
Erste Impfung	55 (2,8)	24 (3,7)
Zweite Impfung	49 (2,5)	12 (1,8)
Schwellung		
Erste Impfung	24 (1,2)	14 (2,1)
Zweite Impfung	28 (1,4)	3 (0,5)
Rötung		
Erste Impfung	65 (3,3)	23 (3,5)
Zweite Impfung	58 (2,9)	10 (1,5)

Tab. 1 | Tagebucheinträge zur lokalen Verträglichkeit am Tag nach der Impfung (Daten aus der sogenannten Sicherheitspopulation; aus Tauber et al., 2008)

Tabelle 2

Author, Year	Other study ID	Setting	Subjects	Design	Intervention	Comparison	Relevant Out-come(s)	Out-come(s) Analysis	Other Flaviviridae considered
Alberer, 2014	V59_38	Germany, Czech Republic; 4 study centers	18 – 60 y	Phase IIIb open-label, randomized clinical trial	JEV + rabies + MenACWY	3 groups: JEV + rabies rabies alone MenACWY alone	Safety	Adverse events (SAE and AE)	Flavi history excluded
Ayad, 2015	IC51-324	USA, Australia; Germany	9 months 20 y	Phase III, uncontrolled follow-up study	None (IC51 given in parent study IC51-322)	None	Immunoge-nicity; safety	PRNT50, adverse events (SAE and AE)	Flavi not mentioned
Butler, 2017		Texas, USA; hospital	2 months – 16 y	Retrospective chart review; observational study, cross-sectional	IC51 vaccination in unknown dosis	None	Safety	Adverse events (SAE and AE); 42 % only one dose!	Flavi not mentioned
Chan, 2016		Singapore; Singhealth Investigatio-nal Medicine Unit	21 – 50 y	Phase 2, Open-label randomized clinical trial	JE vaccine followed by YF vaccine	YF vaccine alone; Focus of the study was YFV, but: Concerning JEV: YFV was given in different time periods to JEV (1,4,9 months)	Safety	Adverse events (SAE and AE)	''Flavi study'', but conclusion only made for YFV (cross-reac-tive antibodies could enhance the immunoge-nicity of LAV)
Cramer, 2016	IC51-315	Austria and Germany, multi-cente-red study	> 65 y	Phase 4 prospective, open-label single arm study	IC51 vaccination	None (in regards of immunogeni-city: comparison with & without previous TBE vaccination)	Immunoge-nicity (also comparison with TBE vaccinati-on); safety	PRNT50, Adverse events (SAE and AE)	Flavi history and vaccination excluded (except for TBE vaccination > 30d before study); protection 30 % better when TBEV before
Dubischar, 2017[a]	IC51-323	Philippines; 3 study centers	2 months – 18 y	Phase 3 RCT with a dose-finding run-in phase	IC51 vaccination in different doses	HAVRIX 720 or Prevnar vaccine	Immunoge-nicity (results of an interim analysis for the dose-fin-ding phase); safety	PRNT50; Adverse events (SAE and AE)	Flavi: baseline JEV and Dengue was made
Dubischar, 2017[b]	IC51-323	Philippines; 3 study centers	2 months – 18 y	Phase 3 RCT with a dose-finding run-in phase	IC51 vaccination in different doses	HAVRIX 720 or Prevnar vaccine	Immunoge-nicity	PRNT50	Flavi: baseline JEV and Dengue was made
Dubischar-Kastner, 2010	IC51-305	Northern Ireland, Germany; two centers	19 – 72 y	Phase 3 uncontrolled, unblinded follow up study	IC51 booster	Subjects differently vaccinated before (2x6, 1x12 or 1x6 µcg), booster at month 11 vs month 23 vs no booster	Immunoge-nicity; safety	PRNT50, Adverse events (SAE and AE)	Flavi see below*
Eder, 2008	IC51-304	Austria, Germany; 6 study centers	> 18 y	Phase 3 RCT	IC51 vaccination	3 batches of IC51	Safety	Adverse events (SAE and AE)	Flavi not mentioned

Fortsetzung Tab. 2

Author, Year	Other study ID	Setting	Subjects	Design	Intervention	Comparison	Relevant Out-come(s)	Out-come(s) Analysis	Other Flaviviridae considered
Eder, 2011	IC51-311	Austria, Germany; 3 study centres	19–66 y	Phase 3 prospective open-label, follow up study	IC51 booster 15 months after first dose	None	Immunogenicity (also 6+12 months after the booster dose); safety	$PRNT_{50}$, adverse events	Flavi history excluded; flavi vaccination only excluded DURING the study
Erra, 2012		Finland, Sweden; 2 travel clinics	18–72 y	Prospective non-randomized single-blind (serol. analysis) study	IC51 vaccination (basic immunization or booster); JE-MB (basic immunization or booster)	4 groups: - no prior JE vaccine. 1. JE-MB 2. JE-VC - prior vaccination with JE-MB. 3. Booster with JE-MB 4. Booster with JE-VC	Immunogenicity	$PRNT_{50}$	Flavi: see below**
Erra, 2013[a]		Finland, Sweden	> 18 y	Non-randomized follow-up study	none	Former vaccin: (1) JE-VC primary (VC), (2) JE-MB primary, followed by single JE-VC booster (MB-VC), (3) JE-MB primary and single JE-MB booster (MB-MB)	Immunogenicity §	$PRNT_{50}$	Flavi: previous vaccinations (YF and TBE) analysed; JE history excluded
Erra, 2013[b]		Finland, Sweden	> 18 y	Follow up study	none	Former vaccination with Ixiaro (SA 14-14-2) or GCC (Nakayama)	Immunogenicity §§	$PRNT_{50}$	Flavi not mentioned
Haas, 2008	IC51-310	Austria, Germany	> 18	Phase 3 RCT, double-blinded	IC51 vaccination	3 batches of IC51	Safety	Adverse events (SAE and AE)	Flavi not mentioned
Hatzenbichler, 2014	IC51-314	Austria, Germany	> 18	Phase 3 non-randomized study	IC51 vaccination	IC51 12, 18, and 24 months post filling	Safety	Adverse events (SAE and AE)	Flavi not mentioned
Jelinek, 2015	V49_23	Austria, Germany, Switzerland	> 18–≤ 65	Phase 3 randomized trial	IC51 vaccination	4 groups: 1. JE+rabies-standard 2. JE+rabies-accelerated 3. JE-standard 4. rabies standard	Immunogenicity; safety	$PRNT_{50}$, Adverse events (SAE and AE)	Flavi: prior JEV excluded
Jelinek, 2018	IC51-322	USA, Australia, Denmark, Sweden, Germany; 11 sites	2 months – 18 y	Phase 3 uncontrolled, open-label study	IC51 0.25 mL or 0.5 mL	None	Immunogenicity in subset; safety	$PRNT_{50}$, Adverse events (SAE and AE)	Flavi infection or vaccination excluded
Kadlecek, 2018	IC51-325	Philippines	2 months – 18 y	Phase 3 randomized, controlled open-label study	IC51 booster after initiation of primary series	No booster	Immunogenicity; safety	$PRNT_{50}$ up to 3 ys after primary series; Adverse events (SAE and AE)	Flavi not mentioned

Fortsetzung Tab. 2

Author, Year	Other study ID	Setting	Subjects	Design	Intervention	Comparison	Relevant Out-come(s)	Out-come(s) Analysis	Other Flaviviridae considered
Kalten-böck, 2009	IC51-308	Austria, Germany; 3 centers	> 18	Phase 3 single-blind, randomized, controlled study	IC51, alone or with HAVRIX	IC51, alone or with HAVRIX	Immunoge-nicity; safety	$PRNT_{50}$, Adverse events (SAE and AE)	Flavi history excluded, vaccination against YFV, JEV excluded
Kalten-böck, 2010	IC51-221	India	1–3 y	Phase 2 open-label randomized study	IC51 0.25 mL or 0.5 mL	IC51 0.25 mL or 0.5 mL	Immunoge-nicity; safety	$PRNT_{50}$, Adverse events (SAE and AE)	Flavi history of any or vaccination against JE, YF and Dengue fever
Lyons, 2007		USA	> 18–49 y	Phase 2 randomized, open label, unblinded, single center study	IC51 0.5 mL or 1 mL, 2 or 3 doses	IC51 0.5 mL or 1 mL, 2 or 3 doses	Immunoge-nicity; safety	$PRNT_{50}$, Adverse events (SAE and AE)	Flavi history and vaccination excluded
Paul-ke-Kori-nek, 2015		Austria, Germany; 2 sites	> 18	cross-sectional open-labeled clinical study	None (preceding trial: basic immuniza-tion, booster after 15 months)	None (preceding trial: basic immuniza-tion, booster after 15 months)	Immunoge-nicity after 6 years	$PRNT_{50}$	Flavi: Grouping for vaccination history regarding YF and TBE done
Rabe, 2015		USA	> 17	Surveillance review	None	275,848 JE-VC doses distributed	Safety	Adverse events (SAE and AE)	Flavi not mentioned
Schuller, 2008[a]	IC51-303	Austria, Germany, Romania; 4 centres	> 18	Phase 3 multicenter follow-up study	None	immunogenicity (JE-VAX®) at 6 months	Immunoge-nicity at 6 and 12 months; safety	PRNT50, Adverse events (SAE and AE)	Flavi: 4 subjects (2 %) of the comparative immunogenicity population received prohibited flavivirus vaccinations during study (TBE, YF, JE); all 4 seroconverted, with $PRNT^{50}$ values within the overall distribution
Schuller, 2008[b]	IC51-301	US, Germany, Austria	>18	Phase 3 active-control-led, randomi-zed, observer-blind trial	IC51	JE-VAX®	Immunoge-nicity; safety	PRNT50, Adverse events (SAE and AE)	Flavi: Subjects analysed for possible effect of prior, vaccine-in-duced TBE immunity on SCR (13 % had previous TBE vaccination)
Schuller, 2009	IC51-309	Germany, Northern Ireland; 2 centres	> 18	Phase 3 randomized, observer-blind, controlled study	IC51 (1 or 2 x 0,5 mL or 1 x 1 mL)	3 groups: 1. 1 × 12µg 2. 2 × 6 µg compared to 3. 1 × 6 µg	Immunoge-nicity; safety	PRNT50, Adverse events (SAE and AE)	Flavi history of any or vaccination against JE, YF and Dengue fever excluded3-

Fortsetzung Tab. 2

Author, Year	Other study ID	Setting	Subjects	Design	Intervention	Comparison	Relevant Out-come(s)	Out-come(s) Analysis	Other Flaviviridae considered
Tauber, 2007	IC51-301	USA, Germany, Austria; sites in US and G were professional site-manage-ment organisa-tions for clinical trials	> 18	Phase 3 non-inferiority, randomised observer-blin-ded, controlled trial	IC51	JE-VAX®	Immunoge-nicity; safety	PRNT^{50}, Adverse events (SAE and AE)	Flavi history of any or vaccination against JE, YF excluded
Tauber, 2008	IC51-302	Australia, Austria, Germany, Israel,US, New Zealand, Romania; 39 centres	> 18	Phase 3 randomized, double-blind, placebo-control-led	IC51	Placebo	Safety	Adverse events (SAE and AE)	Flavi: Only previous JEV excluded
Taucher, 2017	IC51-401	USA; military personnel	> 17	Surveillance Review	IC51	JE-VAX®	Safety	Adverse events (Tier 1 and 2)	Flavi not mentioned
Taucher, 2019	IC51-303	Australia, Austria, Germany, Israel, US, NZ, Romania	> 18	Follow up study	None	None (Immunogeni-city compared between subjects with or without prior TBE vaccination)	Immunoge-nicity (months 24, 36, 48 and 60); safety	PRNT^{50}, Adverse events (SAE and AE)	Flavi: data compare persistence of protective antibodies against JE in people with or without TBE vaccination
Walker, 2018		USA	> 17 y	Surveillance review	None	802,229 doses distributed	Safety	Adverse events (SAE and AE)	Flavi not mentioned
Wool-pert, 2012		USA; Military personnel	>19-41 y	prospective, observational clinical trial	IC51	Immunogenicity of IC 52 (2 doses) after previously either 2 doses of JE-MB or naive	Immunoge-nicity; safety	PRNT^{50}, Adverse events (SAE and AE)	Flavi not mentioned

Tab. 2 | Overview of included studies

* Dubischar-Kastner, 2010: With respect to DENV serology, the indirect DENV IgG Indirect Enzyme-linked Immunosorbent Assay method used in this study has limited specificity for DENV and may have resulted in false-positive results because of cross reaction with other flaviviruses. However, restricted by the limited amount of blood that could be drawn in children, we were limited to a test that requires less volume. Only 11 subjects overall were JEV+ but tested DENV–.In contrast, there was a significant proportion of about 30 % that tested positive for DENV but were negative for JEV, indicating that those subjects may truly have had exposure to DENV only, without exposure to JEV. Investigation of the impact of previous JEV or DENV infection on the immune response to JE vaccination was done by stratifying subjects according to their prevaccination serostatus for JEV and DENV. There was no significant association with pre-existing JEV immunity on the response to vaccination when measured at day 56.

** Erra 2012: When subgroups of volunteers with a history of previous vaccination against tick-borne encephalitis (TBE) or yellow fever (YF) were compared to those without such history, no differences were observed for 3 of the 4 vaccine groups (data not shown). In group VC, travelers with a previous YF vaccination history had higher endpoint antibody titers than subjects without a history of YF vaccination. We ' observed no differences in JEV antibody responses with respect to TBE vaccination status, yet the uneven distribution and small number of previous or simultaneous TBE vaccinations limits firm conclusions based on these data.

§ Erra, 2013[a]: Immunogenicity test against seven JEV strains representing genotypes I – IV

§§ Erra, 2013[b]: Immunogenicity of Ixiaro against heterologous genotypes, cross-genotype immunogenicity of inactivated JEV

Immuno-genicity	Study	RoB arising from randomi-zation process	RoB due to deviations from intended interventions	RoB due to missing outcome data	RoB in outcome measurement	RoB in selective reporting	Overall RoB
	Alberer, 2014	-	-	-	-	-	-
	Dubischar, 2017[a,b]	-	-	-	-	++	++
	Jelinek, 2015	-	-	-	-	-	-
	Kadlecek, 2018	-	-	-	-	++	++
	Kaltenböck, 2009	-	-	-	-	+	+
	Kaltenböck, 2010	-	-	-	-	+	+
	Lyons, 2007	-	-	-	-	+	+
	Schuller, 2009	-	-	-	-	+	+
	Schuller, 2008[b]	-	-	+	-	++	++
	Tauber, 2007	-	-	+	-	++	++

Safety	Study	RoB arising from randomi-zation process	RoB due to deviations from intended interventions	RoB due to missing outcome data	RoB in outcome measurement	RoB in selective reporting	Overall RoB
	Alberer, 2014	+	-	-	-	-	+
	Chan, 2016	+	+	-	-	-	+
	Dubischar, 2017[a]	+	-	-	-	++	++
	Eder, 2008	+	-	-	-	++	++
	Haas, 2008	+	-	-	-	++	++
	Jelinek, 2015	+	-	-	-	-	+
	Kadlecek, 2018	+	+	-	-	++	++
	Kaltenböck, 2009	-	-	-	-	+	+
	Kaltenböck, 2010	+	-	-	-	+	+
	Lyons, 2007	-	-	-	-	+	+
	Schuller, 2009	++	-	-	-	+	++
	Schuller, 2008[b]	-	++	+	-	++	++
	Tauber, 2007	-	++	+	-	++	++
	Tauber, 2008	-	-	-	-	++	++

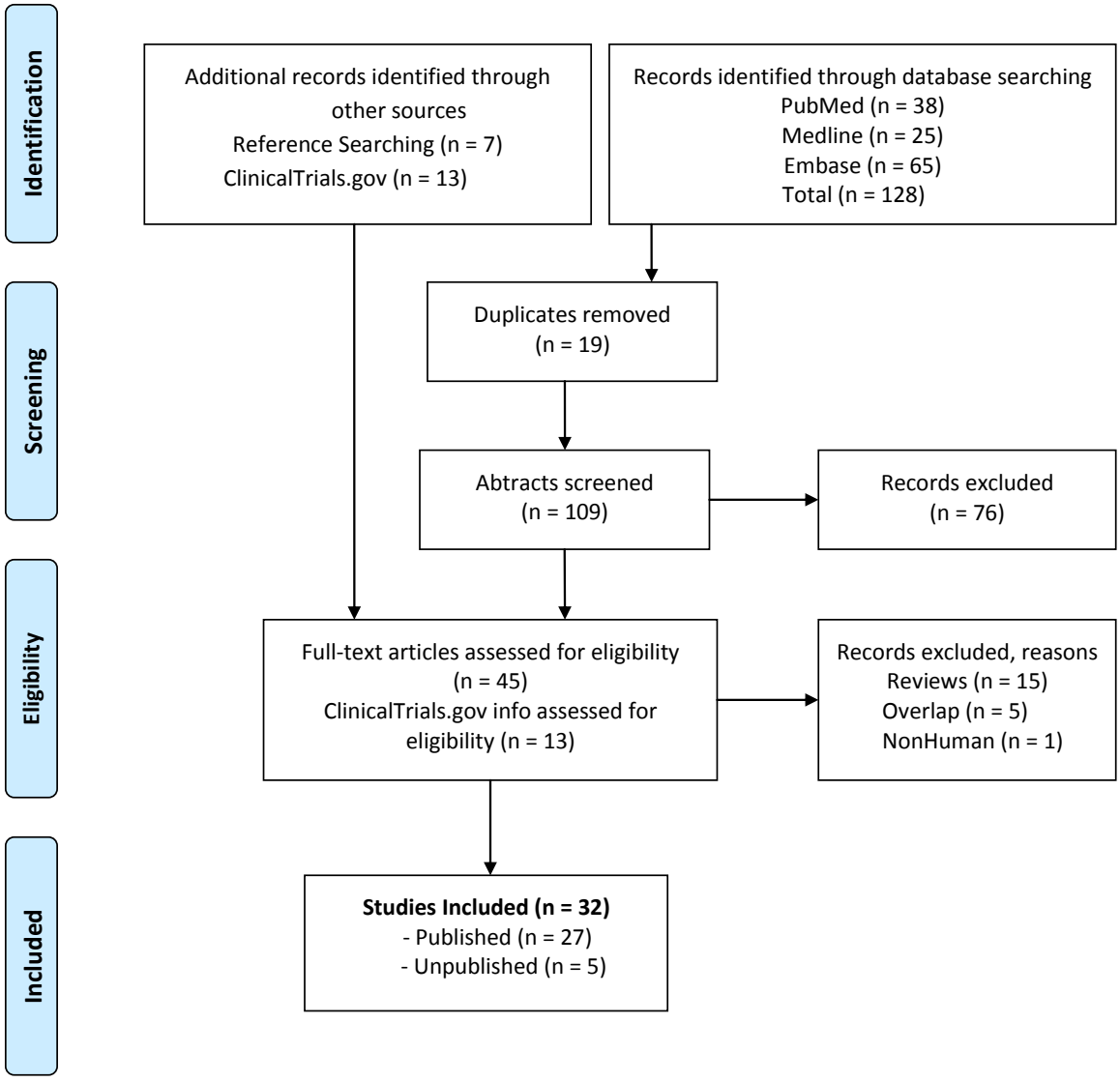
Tab. 3 | Cochrane risk of bias (ROB) assessment for randomised studies, ranging from low (-) to critical (++)

Immunogenicity	Study	Bias Due to Confounding	Bias Due to Selection of Participants into the Study	Bias in Classification of Interventions	Bias due to Deviations from the Intended Interventions	Bias due to Missing Data	Bias due to Measurement of Outcomes	Bias due to Selection of Reported Result	Overall bias
	Ayad, 2015	x	-	-	-	-	-	xx	xx
	Cramer, 2016	x	-	-	-	-	-	x	x
	Dubischar-Kastner, 2010	x	-	-	-	-	-	x	x
	Eder, 2011	x	-	-	-	-	-	-	x
	Erra, 2012	x	-	-	-	-	-	-	x
	Erra, 2013	x	-	-	-	-	-	-	x
	Erra, 2013	x	-	-	-	-	-	-	x
	Jelinek, 2018	x	-	-	-	-	-	xx	xx
	Paulke-Korinek, 2015	x	-	-	-	-	-	x	x
	Schuller, 2008[a]	x	-	-	-	-	-	xx	xx
	Taucher, 2019	x	-	-	-	-	-	xx	xx
	Woolpert, 2012	x	-	-	-	x	-	-	x

Safety	Study	Bias Due to Confounding	Bias Due to Selection of Participants into the Study	Bias in Classification of Interventions	Bias due to Deviations from the Intended Interventions	Bias due to Missing Data	Bias due to Measurement of Outcomes	Bias due to Selection of Reported Result	Overall bias
	Ayad, 2015	x	-	-	-	-	xx	xx	xx
	Butler, 2017	x	-	-	-	-	xx	x	xx
	Cramer, 2016	x	-	-	-	-	xx	x	xx
	Dubischar-Kastner, 2010	x	-	-	-	-	xx	x	xx
	Eder, 2011	x	-	-	-	-	xx	-	xx
	Hatzenblicher, 2014	x	-	-	-	-	xx	-	xx
	Jelinek, 2018	x	-	-	-	-	xx	xx	xx
	Rabe, 2015	x	-	-	-	-	xx	-	
	Schuller, 2008[a]	x	-	-	-	-	x	-	x
	Taucher, 2017	x	-	-	-	-	xx	xx	xx
	Taucher, 2019	x	-	-	-	-	x	-	x
	Walker, 2018	x	-	-	-	-	xx	-	xx
	Woolpert, 2012	x	-	-	-	x	-	-	x
	Tauber, 2008	-	-	-	-	xx	xx		

Tab. 4 | ROBINS-I risk of bias assessment for non-randomized studies, ranging from low (-) to critical (xxxx)

PRISMA – Abb. 1: Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Abb. 1 | PRISMA Flow Diagram