Lancet Infectious Diseases

JL Mostaza Bibliográfica 4/10/2019







Vacunas frente a Herpes zoster (1)

Immunogenicity and safety of the **adjuvanted recombinant** zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis.

Lancet Infect Dis. 2019 Sep;19(9):988-1000.

Safety and efficacy of **inactivated** varicella zoster virus vaccine in immunocompromised patients with malignancies: a two-arm, randomised, double-blind, phase 3 trial.

Lancet Infect Dis. 2019 Sep;19(9):988-1000.







Vacunas frente a Herpes zoster 3

- Incidencia HZ: 3,2-4,5/ 1000 personas/año.
 - 10% desarrollan neuralgia postherpética
 - 5% experimentan recidiva
- Vacunación con virus atenuados: Zostavax[®].
 - Misma cepa que vacuna de varicela pero mayor potencia.
 - Efectividad 51%.
 - Contraindicada en inmunodeprimidos.
- Nuevas vacunas: "no contraindicadas en inmunodeprimidos".
 - Recombinante: Shingrix[®]
 - Glicoproteína E + adyuvante (AS01B).
 - Efectividad 90%.
 - Virus atenuados (Zostavax[®]) inactivados por irradiación γ.







Safety and efficacy of inactivated varicella zoster virus vaccine in immunocompromised patients with malignancies: a two-arm, randomised, double-blind, phase 3 trial

Kathleen M Mullane, Vicki A Morrison, Luis H Camacho, Ann Arvin, Shelly A McNeil, Jessie Durrand, Bernadette Campbell, Shu-Chih Su, Ivan S F Chan, Janie Parrino, Susan S Kaplan, Zoran Popmihajlov, Paula W Annunziatoon behalf of the V212 Protocol 011 Trial Team.

Funding: Merck & Co, Inc.

Lancet Infect Dis. 2019 Sep;19(9):1001-1012.







Background

- Patients with malignancy have an increased risk of Herpes zoster (increased risk of developing severe and life-threatening complications).
 - Solid tumour (chemotherapy): 15 cases/1000 person-years.
 - Haematological malignancies: 31 cases/1000 person-years
 - General adult population > 50 years: 9 cases/1000 person-years.
- We aimed to investigate...
 - Efficacy and safety of an inactivated varicella zoster virus (VZV) vaccine for Herpes zoster prevention
 - Patients with solid tumour or haematological malignancies.







Methods 1

- Phase 3, two-arm, randomised, double-blind, placebo-controlled, multicentre trial with an adaptive design.
 - 329 centres across 40 countries.
- Adult patients with a history of varicella infection or be seropositive for antibodies to VZV.
 - Solid tumour malignancies receiving chemotherapy.
 - Haematological malignancies, with or without chemotherapy.
- Randomly assigned (1:1):
 - 4 doses of VZV vaccine inactivated by γ irradiation (30 days apart).
 - Placebo.
- Were masked to the group assignment.
 - Patients, investigators, trial site staff, clinical adjudication committee, and sponsor's clinical and laboratory personnel.







Trial with an adaptive design



- Refining the sample size.
- Abandoning treatments or doses.
- Changing the allocation ratio of patients to trial arms.
- Identifying patients most likely to benefit and focusing recruitment efforts on them.
- Stopping the whole trial at an early stage for success or lack of efficacy.







Methods 2

- Primary efficacy endpoint:
 - Herpes zoster incidence in patients with solid tumour malignancies receiving chemotherapy.
 - In the modified intention-to-treat population
 - Defined as all randomly assigned patients who received at least one dose of inactivated VZV vaccine or placebo.
- Primary safety endpoint:
 - Serious adverse events up to 28 days after the fourth dose.
 - Safety endpoints were assessed in all patients who received at least one dose of inactivated VZV vaccine or placebo and had follow-up data.
- Trial is registered: (NCT01254630 and EudraCT 2010-023156-89).







Findings

- June 27, 2011, and April 11, 2017.
- 5286 patients were randomly...
 - VZV vaccine inactivated by γ irradiation (n=2637).
 - Placebo (n=2649).
- The haematological malignancy arm was terminated early because of evidence of futility at a planned interim analysis.
 - All prespecified haematological malignancy endpoints were deemed exploratory.
- In patients with solid tumour malignancies in the modified intentionto-treat population, confirmed herpes zoster occurred:
 - VZV vaccine recipients: 22 of 1328 (6.7 per 1000 person-years).
 - Placebo recipients: 61 of 1350 (18.5 per 1000 person-years).
 - Estimated vaccine efficacy: $63 \cdot 6\%$ ($97 \cdot 5\%$ CI $36 \cdot 4$ to $79 \cdot 1$).
 - Meeting the prespecified success criterion.







Findings 2

- In patients with solid tumour malignancies, serious adverse events were similar:
 - Vaccine-received: 298 (22.5%) of 1322.
 - Placebo- received: 283 (21.0%) of 1346
 - Risk difference 1.5%, 95% CI -1.7 to 4.6.
- Vaccine-related serious adverse events <1% in each treatment group.
- Vaccine-related injection-site reactions were more common in the vaccine group than in the placebo group.
- In the haematological malignancy group...
 - VZV vaccine was well tolerated and estimated vaccine efficacy against herpes zoster was 16.8% (95% CI –17.8 to 41.3).







	Patients with solid tumo	ur malignancies	Patients with haematological malignancies		
	InactivatedVZV vaccine (n=1348)	Placebo (n=1364)	Inactivated VZV vaccine (n=1288)	Placebo (n=1285)	
Age, years	57-6 (11-5)	57-7 (11-5)	61.0 (14-9)	61-4 (14-5)	
<50 years	299 (22-2%)	320 (23-5%)	235 (18-2%)	223 (17-4%)	
≥50 years	1049 (77-8%)	1044 (76-5%)	1053 (81-8%)	1062 (82-6%)	
Sex					
Men	481 (35-7%)	472 (34-6%)	760 (59-0%)	762 (59-3%)	
Women	867 (64-3%)	892 (65-4%)	528 (41.0%)	523 (40.7%)	
Race					
White	1044 (77-4%)	1031 (75-6%)	976 (75-8%)	986 (76-7%)	
Multiracial	144 (10-7%)	159 (11-7%)	157 (12-2%)	141 (11-0%)	
Black or African American	86 (6-4%)	92 (6-7%)	41 (3-2%)	57 (4-4%)	
Asian	55 (4-1%)	64 (4-7%)	110 (8.5%)	94 (7-3%)	
Other or not reported	19 (1-4%)	18 (1-3%)	4 (0-3%)	7 (0.5%)	
Ethnicity					
Not Hispanic or Latino	971(72.0%)	979 (71-8%)	985 (76-5%)	979 (76-2%)	
Hispanic or Latino	356 (26-4%)	366 (26-8%)	286 (22-2%)	290 (22-6%)	
Unknown, not reported, or missing	21 (1-6%)	19 (1-4%)	17 (1-3%)	16 (1-2%)	
Primary diagnosis*					
Breast cancers	499/1328 (37-6%)	496/1350 (36-7%)	0	0	
Colon, colorectal, and rectal cancers	289/1328 (21-8%)	279/1350 (20-7%)	0	0	
Lung cancers	152/1328 (11-4%)	146/1350 (10-8%)	0	0	
Ovarian cancers	64/1328 (4-8%)	69/1350 (5-1%)	0	0	
Chronic lymphocytic leukaemia	0	0	324/1277 (25-4%)	343/1275 (26-9%)	
Plasma cell myelomas	0	0	199/1277 (15-6%)	197/1275 (15-5%)	
Chronic myeloid leukaemias	0	0	154/1277 (12-1%)	152/1275 (11-9%)	
Non-Hodgkin lymphomas	0	0	116/1277 (9-1%)	93/1275 (7-3%)	
Other	324/1328 (24-4%)	360/1350 (26-7%)	484/1277 (37-9%)	490/1275 (38-4%)	
Most frequent concornitant medicatio	ns*†	1997 Too 19 20 10 2 19 10 2 10 10 2 10 10 10 10 10 10 10 10 10 10 10 10 10			
Anti-neoplastic agents	1292/1328 (97-3%)	1315/1350 (97-4%)	702/1277 (55-0%)	682/1275 (53-5%)	
Anti-emetics and anti-nauseants	996/1328 (75-0%)	1021/1350 (75-6%)	316/1277 (24-7%)	329/1275 (25-8%)	
Systemic corticosteroids	972/1328 (73-2%)	981/1350 (72-7%)	479/1277 (37.5%)	497/1275 (39-0%)	
Drugs for acid-related disorders‡	803/1328 (60-5%)	815/1350 (60-4%)	567/1277 (44-4%)	530/1275 (41-6%)	
Analoesics	737/1328 (55-5%)	754/1350 (55-9%)	785/1277 (61-5%)	755/1275 (59-2%)	



B Patients with haematological malignancies



Efficacy endpoints in patients with solid tumour malignancies in the modified intention-to-treat population

	Inactiv	ated VZV vaccine (n	=1328)	Placebo (n=1350) Estimated vaccine		Estimated vaccine efficacy	
	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (CI)	n	Total follow-up time (person-years)	Observed incidence per 1000 person-years (CI)	
Primary efficacy endpoint*							
Confirmed herpes zoster	22	3266	6-7 (97-5% Cl 4-2 to 10-2)	61	3305	18-5 (97-5% Cl 14-1 to 23-7)	63-6% (97-5% CI 36-4 to 79-1)
Secondary efficacy endpoints							
Moderate to severe herpes zoster-associated pain	7	3266	2-1 (95% CI 0-9 to 4-4)	31	3305	9-4 (95% Cl 6-4 to 13-3)	77-1% (95% Cl 48-0 to 89-9)
Herpes zoster complications	1	3266	0-3 (95% CI 0-01 to 1-7)	8	3305	2-4 (95% CI 1-1 to 4-8)	87-4% (95% Cl -0-5 to 98-4)
Post-herpetic neuralgia	1	3266	0-3 (95% CI 0-01 to 1-7)	4	3305	1-2 (95% Cl 0-3 to 3-1)	74-6% (95% CI-127-5 to 97-2)

Data are as specified. VZV-varicella zoster virus. *Per original protocol.







	Patients with solid tumour malignancies receiving chemotherapy			Patients with haematological malignancies		
	Inactivated zoster vaccine (n=1322)	Placebo (n=1346)	Risk difference versus placebo	Inactivated zoster vaccine (n=1274)	Placebo (n=1274)	Risk difference versus placebo
Patients with one or more adverse events	1086 (82-1%)	1077 (80-0%)	2·2% (-0·8 to 5·1)	1030 (80-8%)	911 (71-5%)	9·3% (6·0 to 12·5)
Systemic adverse events	1006 (76-1%)	1057 (78-5%)	-2.4% (-5.6 to 0.7)	902 (70-8%)	866 (68-0%)	2.7% (-0.9 to 6.3)
Vaccine-related adverse event	479 (36-2%)	190 (14-1%)	22-2% (19-1 to 25-4)	570 (44-7%)	216 (17-0%)	28.0% (24.5 to 31.4)
Vaccine-related injection site adverse event	448 (33-9%)	116 (8-6%)	25-4% (22-4 to 28-3)	512 (40-2%)	167 (13-1%)	27-2% (24-0 to 30-5)
Vaccine-related non-injection site adverse event	77 (5-8%)	88 (6-5%)	-0.7% (-2.5 to 1.2)	131 (10-3%)	72 (5:7%)	47% (2.6 to 6.8)
Serious adverse event	298 (22-5%)	283 (21-0%)	1-5% (-1-7 to 4-6)	203 (15-9%)	190 (14-9%)	1-0% (-1-8 to 3-8)
Serious vaccine-related adverse event	2 (0-2%)	0	0·2% (-0·1 to 0·5)	8 (0-6%)	3 (0-2%)	0-4% (-0-1 to 1-0)
Discontinued due to adverse event	29 (2-2%)	23 (1-7%)	0.5% (-0.6 to 1.6)	25 (2-0%)	12 (0.9%)	1·0% (0·1 to 2·0)
Death Data are n (%) or % (95% Cl).	123 (9-3%)	107 (7-9%)	1-3% (-0-8 to 3-5)	35 (2-7%)	34 (2:7%)	0-1% (-1-2 to 1-4)







Interpretation

- The inactivated VZV vaccine:
 - Well tolerated and efficacious for herpes zoster prevention:
 - Solid tumour malignancies receiving chemotherapy.
 - Not efficacious for herpes zoster prevention:
 - Haematological malignancies.







Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis.

Alemnew F Dagnew, Osman Ilhan, Won-Sik Lee, Dariusz Woszczyk, Jae-Yong Kwak, Stella Bowcock, et al.

Funding: Glaxo Smith Kline Biologicals SA.





Lancet Infect Dis. 2019 Sep;19(9):988-1000.



Background

- The adjuvanted recombinant zoster vaccine (Shingrix) can prevent herpes zoster:
 - Older adults.
 - Autologous haemopoietic stem cell transplant recipients.
 - Renal transplant recipients.
 - Solid tumours.
 - People with HIV.
- We evaluated the safety and immunogenicity of this vaccine...
 - Adults with haematological malignancies receiving immunosuppressive cancer treatments.







Methods

- Phase 3, randomised, observer-blind, placebo-controlled study,
- 77 centres worldwide.
- We randomly assigned (1:1) patients with haematological malignancies >18 years to receive:
 - Two doses of the adjuvanted recombinant zoster vaccine.
 - 1–2 months apart during or after immunosuppressive cancer treatments,
 - Placebo.
- We stratified participants according to their underlying diseases.







Methods 2

- Co-primary objectives:
 - Safety and reactogenicity of the zoster vaccine from the first vaccination up to 30 days after last vaccination in all participants.
 - Anti-glycoprotein E humoral immune response.
 - Excluding non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia.
 - Glycoprotein E-specific CD4[2+] T cells.
- Secondary objectives
 - Incidence of herpes zoster cases.
 - Safety.
- Per-protocol cohort analysis
- The study is registered with ClinicalTrials.gov: NCT01767467.
 - EU Clinical Trials Register, number 2012-003438-18.







Findings

- Between March 1, 2013, and Sept 10, 2015.
- 283 in the vaccine group and 279 in the placebo group.
- At month 2, humoral vaccine response
 - Adjuvanted recombinant zoster vaccine:
 - 119 (80·4%, 95% CI 73·1–86·5) of 148 participants
 - Adjusted geometric mean anti-glycoprotein E antibody concentration
 - 23 132·9 mIU/mL (95% CI 16 642·8–32 153·9).
 - Placebo group:
 - 1 (0.8%, 0.0–4.2) of 130 participants.
 - Adjusted geometric mean anti-glycoprotein E antibody concentration
 777.6 mIU/mL (702.8–860.3)
 - Adjusted geometric mean ratio 29.75, 21.09-41.96; p<0.0001.
- Humoral and cell-mediated immune responses persisted above baseline until month 13 in all strata.
 - Vaccine was more reactogenic than placebo.







Findings 2

- Post-hoc analysis: Herpes zoster incidence
 - − Vaccine group: 8.5 per 1000 person-years.
 - Placebo group: 66·2 per 1000 person-years,
 - Efficacy: 87·2% (95% CI 44·3–98·6; p=0·0021)
 - Median follow-up was $11 \cdot 1$ months (IQR $10 \cdot 3 12 \cdot 2$).
- Within 7 days after vaccination
 - Pain was reported by 221 [79.5%] of 278 vaccine group participants and 45 [16.4%] of 274 placebo group participants;
 - Fatigue was reported by 162 [58·3%] of 278 vaccine group participants and 102 [37·2%] of 274 placebo group participants.
- Incidences of adverse events were similar between the groups.
 - Unsolicited or serious adverse events.
 - Potential immune-mediated diseases.
 - Disease-related events.









	Adjuvanted recombinant zoster vaccine (n=283)	Placebo (n=279)
Age at first vaccination (years)	56-8 (15-5)	57-8 (14-9)
Age group (years)		
18-49	74 (26-1%)	73 (26-2%)
≥50	209 (73-9%)	206 (73-8%)
5ex		
Male	169 (59-7%)	165 (59-1%)
Female	114 (40-3%)	114 (40.9%)
thnicity		
American Hispanic or Latino	11 (4.0%)	15 (5-6%)
Not American Hispanic or Latino	261 (96-0%)	253 (94-4%)
Missing	11	11
Geographic ancestry		
African heritage or African American	1 (0-4%)	1(0.4%)
American Indian or Alaska native	0	1(0.4%)
Asian-central or south Asian heritage	5 (1-8%)	6 (2-2%)
Asian-east Asian heritage	57 (21.0%)	60 (22-4%)
Asian—southeast Asian heritage	4 (1.5%)	1(0.4%)
White-Arabic or north African heritage	0	1(0.4%)
White—Caucasian or European heritage	198 (72-8%)	186 (69-4%)
Other	7 (2-6%)	12 (4-5%)
Missing	11	11
Timing of study vaccination		
During cancer therapy course—both doses at least 10 days before and after a chemotherapy cycle	102 (36-0%)	106 (38-0%)
10 days to 6 months after the full cancer therapy course	181 (64-0%)	173 (62.0%)
Haematological malignancy		
Chronic lymphocytic leukaemia	42 (14-8%)	41 (14-7%)
Hodgkin lymphoma	49 (17-3%)	47 (16-8%)
Multiple myeloma	67 (23.7%)	65 (23-3%)
Non-Hodgkin B-cell lymphoma	41 (14-5%)	39 (14-0%)
Non-Hodgkin T-cell lymphoma	13 (4.6%)	16 (5-7%)
Other haematological malignancies	71 (25-1%)	71 (25-4%)
Acute lymphoblastic leukaemia	7 (9.9%)	5(7.0%)
Acute myeloid leukaemia	44 (62-0%)	37 (52-1%)
Myelodysplastic syndrome	12 (16-9%)	18 (25-4%)
Other	8 (11-3%)	11 (15-5%)
Patients who had undergone autologous haemopoietic stem cell transplantation before vaccination (post-hoc analysis)	28 (9.9%)	26 (9-3%)
Patients who had undergone allogeneic haemopoietic stem cell transplantation before vaccination (post-hoc analysis)	19 (67%)	21(7.5%)
Graft-versus-host disease*	3 (15-8%)	4 (19-0%)
Eastern Cooperative Oncology Group performance status		
Fully active†	177 (63.7%)	175 (64-3%)
Restricted in physically strenuous activity‡	94 (33-8%)	89 (32-7%)
Ambulatory and capable of all selfcares	6 (2-2%)	7 (2-6%)
Capable of only restricted selfcare¶	1 (0-4%)	1 (0-4%)
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Interpretation

- Adult population with haematological malignancies is at high risk for herpes zoster.
- The adjuvanted recombinant zoster vaccine is likely to benefit this population.
 - Currently licensed for adults aged 50 years and older.







Varicella zoster virus vaccine in patients with haematological malignancies

Per Ljungman

Ljungman P. Lancet Infect Dis. 2019 Aug 24;19(9):921–2.







- An effective zoster vaccine has been used in elderly people for several years...
 - But there is a risk for severe side effects in immunocompromised people.
- More recently, a subunit vaccine was introduced and has been shown to be effective in the elderly population.
- Alemnew Dagnew and colleagues:
 - Haematological malignancies who were vaccinated with two doses of the adjuvanted recombinant subunit vaccine or placebo either during or after cancer therapy.
 - There were fewer herpes zoster cases among patients who had received two doses of the subunit vaccine compared with those who received placebo (two cases vs 14 cases).
 - Post-hoc analysis showed a protective efficacy of 87.2% (95% CI 44.3– 98.6; p=0.0021) against herpes zoster.

Ljungman P. Lancet Infect Dis. 2019 Aug 24;19(9):921–2.







- A possible patient management strategy would be:
 - To give antiviral prophylaxis during the most intensive immunosuppressive treatment periods
 - And then use an effective and safe vaccine to prevent later varicella zoster virus reactivations.
- Elderly patients with hematological malignancies could safely receive the adjuvanted recombinant vaccine.
- It is unclear if additional doses will be needed to maintain an immune response.

Ljungman P. Lancet Infect Dis. 2019 Aug 24;19(9):921–2.







Herpes zoster in people who are immunocompromised: what are the options for prevention?

Charlotte Warren-Gash, Judith Breuer

Warren-Gash C, Breuer J. Lancet Infect Dis. 2019 Aug 24;19(9):922-4.







- Immunocompromised patients have herpes zoster more frequently and severely than the general immunocompetent population.
- Herpes zoster incidence /1000 person-years at risk:
 - Bone-marrow or stem-cell transplants: 43.03
 - Solid organ transplants: 17.04
 - HIV: 17·43
 - General population: 4.82.
- Complications of herpes zoster are also roughly three times higher in people with HIV than in an age-matched general population.
- Severe immunocompromise is a contraindication to receiving live attenuated varicella zoster virus vaccine.
 - Non-live vaccines are likely to hold the key to preventing herpes zoster in individuals who are immunocompromised.

Warren-Gash C, Breuer J. Lancet Infect Dis. 2019 Aug 24;19(9):922-4.







- Promising efficacy and safety of a γ irradiation-inactivated varicella zoster virus vaccine (vOka strain) in patients with solid tumour malignancies receiving chemotherapy.
 - Herpes zoster incidence was markedly reduced in patients with solid tumour malignancies receiving vaccine vs placebo (22 vs 61 cases; vaccine efficacy 63.6%, 97.5% Cl 36.4 to 79.1).
 - The vaccine did not, however, reduce herpes zoster incidence in 2552 patients with haematological malignancies who received at least one vaccine dose (vaccine e cacy 16.8%, 97.5% CI –17.8 to 41.3).
 - The vaccine was well tolerated.
- Individuals with haematological malignancies appeared to mount an effective immune response to the γ-irradiated vaccine...
 - But, this response did not translate into clinical efficacy.

Warren-Gash C, Breuer J. Lancet Infect Dis. 2019 Aug 24;19(9):922–4.







- Another non-live herpes zoster vaccine (Shingrix; GlaxoSmithKline, King of Prussia, PA, USA) is also undergoing clinical trials in patients who are immunocompromised.
- Licensed to prevent herpes zoster and post-herpetic neuralgia in adults aged 50 years and older,
 - Is highly efficacious in older adults who are immunocompetent (vaccine efficacy of around 90% in all age groups from 50 years).
- Eficacy of this vaccine against incident herpes zoster
 - Haematological malignancies: 87%.
 - Autologous haemopoietic stem-cell transplants: 68%.
 - Renal transplant: 68%.
- The efficacy of the γ irradiation- inactivated vaccine in recipients of autologous haemopoietic stem-cell transplants was 64% in a phase 3 trial.

Warren-Gash C, Breuer J. Lancet Infect Dis. 2019 Aug 24;19(9):922-4.







- Duration of protection conferred by non-live vaccines in individuals who are severely immuno-compromised remains unclear.
- Response to the γ irradiation-inactivated vaccine waned markedly over time, Vaccine efficacy...
 - Months 0-12: 80%
 - > 1 year: 44%.
- Duration of immunity has not yet been reported for the attenuated recombinant vaccine in individuals who are immunocompromised...
 - Vaccine efficacy remains higher than 88% against incident herpes zoster at 4 years in older adults who are immunocompetent.
- In summary...
 - Non-live vaccines offer new hope for preventing herpes zoster and its costly complications in individuals who are immunocompromised.

Warren-Gash C, Breuer J. Lancet Infect Dis. 2019 Aug 24;19(9):922-4.







Lung mass

- 77-year-old man with no history of smoking.
- Cough and low-grade fever.
- CT: mass in his right lung and cancer was suspected.
- Tumour markers were not increased.
 - CEA antigen, cytokeratin 19 fragment, progastrin releasing.
- 1⁸F-fluorodeoxyglucose PET: high uptake was detected at the mass.











Lung mass

- Latex agglutination test: Cryptococcal antigen +.
- Bronchoscopia:
 - Pulmonary cryptococcosis.
 - No tumour cells were detected.
- Therapy:
 - Oral fluconazole 200 mg daily for 9 days, oral voriconazole 600 mg daily for 1 day and then 400 mg daily for 13 days, and intravenous liposomal amphotericin B 400 mg daily for 17 days.
- After day 12 on amphotericin B the patient's chest radiograph and CT showed enlargement of the mass.
 - CT-guided repeat biopsy of the pulmonary mass: pulmonary cryptococcosis
- The man refused to continue therapy and left our hospital.
 - The mass shadow gradually improved with only observation at another hospital.





Masaya Taniwaki. Lancet Infect Dis 2019; 19: 1033



Lung cryptococcosis

- Cryptococcosis: Cryptococcus neoformans and Cryptococcus gattii.
- Cryptococcosis has been increasing worldwide.
- Lung nodule shadows are frequently detected in patients with pulmonary cryptococcosis...
 - But lung mass are very rare.
- Lung cancer is primarily suspected when a lung mass shadow is detected...
 - But, infectious diseases, such as pulmonary cryptococcosis, should be considered among the differential diagnoses.





Masaya Taniwaki. Lancet Infect Dis 2019; 19: 1033


Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study.

Tobias Broger*, Bianca Sossen*, Elloise du Toit, Andrew D Kerkho, Charlotte Schutz, Elena Ivanova Reipold, Amy Ward, David A Barr, Aurélien Macé, Andre Trollip, Rosie Burton, Stefano Ongarello, Abraham Pinter, Todd L Lowary, Catharina Boehme, Mark P Nicol, Graeme Meintjes†, Claudia M Denkinger†

Funding Global Health Innovative Technology Fund, UK Department for International Development, Dutch Ministry of Foreign A airs, Bill & Melinda Gates Foundation, German Federal Ministry of Education and Research, Australian Department of Foreign A airs and Trade, Wellcome Trust, Department of Science and Technology and National Research Foundation of South Africa, and South African Medical Research Council.

T. Broger. Lancet Infect Dis. 2019 Jul 13;19(8):852–61.







Background

- Most tuberculosis-related deaths in people with HIV could be prevented with earlier diagnosis and treatment.
- Only commercially available tuberculosis point-of-care test [AlereLAM] has suboptimal sensitivity.
- The novel Fujifilm SILVAMP TB LAM (FujiLAM) assay has been developed to improve the sensitivity of AlereLAM.
 - Combines a pair of high affinity monoclonal antibodies directed towards largely *MT*-specific lipoarabinomannan epitopes.
- We assessed: diagnostic accuracy of the FujiLAM assay.
 - Detection of tuberculosis in hospital inpatients with HIV.







- Biobanked urine samples obtained from the FIND Specimen Bank (University of Cape Town Biobank)
 - Hospital inpatients (aged ≥18 years) with HIV.
 - Comprehensive work-up was done to identify tuberculosis or alternative diagnoses.
 - 3 independent prospective cohort studies done at two South African hospitals.
- Urine samples were tested using FujiLAM and AlereLAM assays.
 - The conduct and reporting of each test was done blind to other test results.
- The primary objective:
 - Diagnostic accuracy of FujiLAM compared with AlereLAM.







- Cohort 1
 - Symptomatic pulmonary disease thought to have Tbc.
- Cohort 2
 - They were admitted to medical wards whether or not they reported tuberculosis symptoms.
- Cohort 3
 - CD4+ ≤ 350 cells/ μL in whom tuberculosis was considered the most likely diagnosis at presentation.
- Patients excluded: if they were already receiving tuberculosis therapy.
- Test developed:
 - Reference standard testing (enrolment):
 - Sputum, blood, and urine specimens for *M tuberculosis*.
 - Follow-up: additional clinical samples.
- Follow-up: 8 weeks for cohort 1, and 12 weeks for cohorts 2 and 3.







- Definite tuberculosis:
 - Microbiologically confirmed.
- Possible tuberculosis:
 - Clinical or radiological features suggestive of tuberculosis and were started on tuberculosis treatment.
- Not-tuberculosis:
 - Microscopy, cultures, and Xpert test results negative.
- Unclassifiable
 - They did not fall into any of these categories
 - Removed from the main analyses.









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Statistical analysis

• Primary analysis

- 95% Cis of FujiLAM and AlereLAM assays
 - Sensitivity, specificity.
 - Positive and negative predictive value.
 - Positive and negative likelihood ratio.
- Comparison...
 - Microbiological reference standard positive: definite tuberculosis.
 - Composite reference standard: definite + possible tuberculosis.
- Heterogeneity between cohorts: Cochran's Q test.
- Post-hoc analysis
 - Comparative diagnostic yield of a single (Samples collected within the first 24h of presentation).
 - FujiLAM, AlereLAM, sputum Xpert, urine Xpert, and sputum smear microscopy test.











Demographic and clinical characteristics

	Cohort 1 (n=96)	Cohort 2 (n=364)	Cohort 3 (n=508)	All patients (n=968)	
Age, years	35 (31-43)	36 (29-42)	35 (30-43)	35 (30-42)	
Sex					
Women	51 (53%)	218 (60%)	254 (50%)	523 (54%)	
Men	45 (47%)	146 (40%)	254 (50%)	445 (46%)	
Positive WHO tuberculosis symptom screen	96 (100%)	329 (90%)	508 (100%)	933 (96%)	
History of tuberculosis	52 (54%)	162 (45%)	225 (44%)	439 (45%)	
Antiretroviral therapy	64 (67%)	153 (42%)	177 (35%)	394 (41%)	
CD4 count, cells per µL	113 (40-262)	153 (53-313)	59 (23-122)	86 (33-190)	
Diagnosis					
Definite tuberculosis	47 (49%)	138 (38%)	415 (82%)	600 (62%)	
Possible tuberculosis	3 (3%)	37 (10%)	51 (10%)	91 (9%)	
Not tuberculosis	46 (48%)	189 (52%)	42 (8%)	277 (29%)	
CD4 count, cells per µL					
0-100	44 (46%)	135 (37%)	337 (66%)	516 (53%)	
101-200	19 (20%)	82 (23%)	115 (23%)	216 (22%)	
>200	30 (31%)	145 (40%)	56 (11%)	231 (24%)	
Unknown	3 (3%)	2 (1%)	0	5 (1%)	
Outcome at 3 months					
Died within 3 months	1(1%)	19 (5%)	85 (17%)	105 (11%)	
Alive	58 (60%)	336 (92%)	416 (82%)	810 (84%)	
Lost to follow-up	0	9 (2%)	7 (1%)	16 (2%)	
No follow-up	37 (39%)	0	0	37 (4%)	
Data are median (IQR), or n (%).					







	rest	n	IP	FP	FN	IN	Sensitivity (95%-CI)	specinicity (95% CI)
MRS	FujiLAM	968	455	33	145	335		♦ 90-8% (86-0 to 94-4)
	AlereLAM	968	268	18	332	350	42-3% (31-7 to 51-8)	-+ 95-0% (87-7 to 98-8)
	Difference						28.1%	-4-2%
CRS								
	Fujilam	968	477	11	214	266	64-9% (50-1 to 76-7)	+ 95-7% (92-0 to 98-0)
	AlereLAM	968	281	5	410	272	38-2% (28-1 to 47-3)	 98-2% (95-7 to 99-6)
	Difference						→ 26-7%	-2.5%
B								
MRS							5	
Cohort 1	FujiLAM	96	28	4	19	45	- 59-6% (45-3 to 72-4) -	
	AlereLAM	96	15	1	32	48	31-9% (20-4 to 46-2)	-+ 98-0% (89-3 to 99-6
1-1127-1127	Difference			47875		2,212,22	→ 27-7% (16-9 to 41-8)	-6-2% (-17-6 to 3-9
Cohort 2	FujiLAM	364	91	18	47	208		◆ 92-0% (87-8 to 94-9
	AlereLAM	364	61	7	77	219	44-2% (36-2 to 52-5)	♦ 96-9% (93-7 to 98-5)
01242V/12017	Difference	11225386	-	do 11	2011.54	200	→ 21.7% (147 to 29.7)	-4-9% (-9-3 to -1-0)
Cohort 3	FujiLAM	508	336	11	79	82	★ 81-0% (76-9 to 84-5)	► 88.2% (80.1 to 93.3)
	AlereLAM	508	192	10	223	83	46-3% (41-5 to 51-1) -	♦- 89-2% (81-3 to 94-1)
	Difference						347% (30-1 to 39-5)	-1.0% (-9-4 to 7-2)
Cohorta	Ford And	05	- 20		- 14	~	F 09 (44 3 to 70 ()	00 [24 /00 [10 0 0 0
Conorti	FUJILAM	96	29	3	21	43	- 58-0% (44-2 to /0-6) -	→ 93.5% (82.5 to 9/.8) 93.5% (82.5 to 9/.8)
	AlefeLAW	96	15	1	35	45	30-0% (19-1 to 43-8)	
C 1 1 2 2	Difference	2220	122	20	100	- 0-	→ 28-0% (1/·5to 41·7)	-4·3% (-15·8 to 5·9)
Cohort 2	FUILAM	364	103	6	72	183	58-9% (51-5 to 65:9)	♥ 96-8% (93-2 to 98-5)
	AlereLAM	364	64	4	m	185	36-6% (29-8 to 43-9)	 9/-9% (94-7 to 99-2 14% (4.01-3.4)
61.45	Difference	r.0.0	2.02	127	2.12	14	-+1 22-3% (15-6 to 29-4)	-1-1% (-4-9 to 2-6)
Conort 3	FUJILAM	508	345	2	1/1	40		95-2% (84-2 to 98-/)
	Difference	500	202	0	204	42	43-3% (36-9 to 4/-9)	
	Difference						307 % (20 2 10 33 3)	-4-030 (-15-0 (0 4-0)
С								
MRS								
0-100 cells per µL	Fujilam	516	332	20	49	115		► 85-0% (75-8 to 91-7)
	AlereLAM	516	221	8	160	127		→ 94-1% (88-3 to 97-7)
	Difference						∢ → 26-9%	-9-1%
101-200 cells per µl.	FujiLAM	216	83	9	49	75	← 60-6% (44-4 to 72-5)	← 89-6% (78-5 to 98-1)
	AlereLAM	216	35	7	97	77	26-4% (15-2 to 38-9)	+ 92-8% (69-2 to 99-9)
	Difference						→ 34-2%	-3·2%
>200 cells per µL	FujiLAM	231	37	4	46	144	44-0% (29-7 to 58-5)	→ 97.0% (92.5 to 99.3)
	AlereLAM	231	10	3	73	145	12-2% (4-6 to 23-7)	
	Difference						31-8%	-0.2%
CRS								
0-100 cells per µL	FujiLAM	516	344	8	76	88		♦ 91-2% (83-1 to 96-3)
	AlereLAM	516	226	3	194	93	← 53·1% (40·7 to 63·6)	+ 96-6% (91-0 to 99-3)
	Difference						4 → Z7-5%	-5-4%
	FujiLAM	216	91	1	66	58	♦ 55-7% (39-9 to 67-6)	🔶 97-8% (90-6 to 99-9)
101-200 cells per µl	AlereLAM	216	41	1	116	58	25-3% (15-3 to 35-6)	-+ 97-8% (90-6 to 99-9)
101–200 cells per µl.							▶ 30-4%	0-0%
101–200 cells per µl.	Difference						35.5% (22.4 to 50.4)	08 30 (03 8 to 00 0)
101-200 cells per µL >200 cells per µL	Difference FujiLAM	231	39	2	71	119	22.2.4.4.4.2.4.1	 90-2% (93-8 to 99-9)
101-200 cells per µL >200 cells per µL	Difference FujiLAM AlereLAM	231 231	39 12	2	71 98	119 120	11-3% (2-3 to 28-7)	 98-9% (95-0 to 100)
101-200 cells per µL »200 cells per µL	Difference FojiLAM AlereLAM Difference	231 231	39 12	2	71 98	119 120	11-3% (2-3 to 28-7) 24-2%	 98-2% (93-8 to 99-9) 98-9% (95-0 to 100)

Number of microbiologically confirmed tuberculosis diagnoses detected by each diagnostic test on samples obtained within 24 h of hospital admission.



Junta de

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B Patients with microbiologically confirmed tuberculosis and CD4 ≤100 cells per µL (n=74)



Diagnosticyleid

- Urine FujiLAM 79-7% (59/74)
- Urine AlereLAM 64-9% (48/74)
- Urine Xpert 58-1% (43/74)
- Sputum Xpert 24-3% (18/74)
- Sputum smear microscopy 18-9% (14/74)
- Tuberculosis cases missed 9-5% (7/74)



Findings

- April 18, 2018, and May 3, 2018,
- Urine samples from 968 hospital inpatients with HIV.
 - Median CD4 count: 86 cells/μL.
- Prevalence of microbiologically-confirmed tuberculosis: 62%.
- Microbiological reference standard
 - Estimated sensitivity...
 - FujiLAM: 70·4% (95% CI 53·0 to 83·1).
 - AlereLAM: 42·3% (31·7 to 51·8).
 - Estimated specificity
 - FujiLAM: 90.8% (86.0 to 94.4).
 - AlereLAM: 95·0% (87·7–98·8).
 - Positive likelihood ratios
 - FujiLAM: 8·9–18·5
 - AlereLAM: 13·8–17·3
 - Negative likelihood ratios.
 - FujiLAM: 0·3–0·4.
 - AlereLAM: 0.6–0.7.







Within the first 24 h of admission...

- A combination of sputum Xpert and FujiLAM 102 (72%) of 141 microbiologically confirmed cases.
- A combination of sputum smear microscopy and FujiLAM
 - 98 (70%) of 141 diagnoses.









Nomograma de Fagan

Positive likelihood ratios FujiLAM: 8·9–18·5 AlereLAM: 13·8–17·3 Negative likelihood ratios. FujiLAM: 0·3–0·4. AlereLAM: 0·6–0·7.



Razón de verosimilitud (likelihood ratio)

Tabla 1Rangos de valores de likelihood ratio y su impactoen utilidad clínica						
LR positivo	LR negativo	Utilidad				
10	<0,1	Altamente relevante				
5-10	0,1-0,2	Buena				
2-5	0,5-0,2	Regular				
<2	> 0,5	Mala				



Interpretation

- In comparison to AlereLAM, FujiLAM offers superior diagnostic sensitivity, while maintaining specificity.
 - It could transform rapid point-of-care tuberculosis diagnosis for hospital inpatients with HIV.
- The applicability of FujiLAM for settings of intended use requires prospective assessment.







A new point-of-care test to diagnose tuberculosis

- Tuberculosis:
 - 1.6 million deaths.
 - Surpassed HIV/AIDS to become the leading infectious cause of mortality worldwide.
- Approximately 36% of tuberculosis cases each year (around 3.5 million cases) are not diagnosed.
- Current diagnostic tools rely on sputum-based testing.
 - Suboptimal diagnostic sensitivity.
 - Especially in immunocompromised people with HIV.
- FujiLAM assay includes novel monoclonal antibodies and enhanced detection technology to enable higher diagnostic sensitivity.

Drain PK. Lancet Infect Dis. 2019 Jul 22;19(8):794-6.







Migratory eruption

- A 33-year-old healthy man, after a holiday in Cambodia.
- 4-week history of an intensely pruritic eruption (right leg).
 - Migratory and showed daily, regional progression.
- On examination:
 - Serpiginous, erythematous, and raised tracts with crusting.



Astrid-Helene Ravn Jørgensen. Lancet Infect Dis. 2019 Aug 17;19(9):1034.







Migratory eruption





Astrid-Helene Ravn Jørgensen. Lancet Infect Dis. 2019 Aug 17;19(9):1034.





Migratory eruption

- On examination:
 - Serpiginous, erythematous, and raised tracts with crusting were noted on the entire lateral side of the affected leg, which is clinically diagnostic of cutaneous larva migrans.
- A swab test for microbiological testing: MRSA.
- Treatment:
 - Clindamycin for 10 days and ivermectin.
- At 3 weeks follow-up, the lesion showed almost complete resolution.







Cutaneous larva migrans

- Penetration and migration of larvae within the epidermis of human skin.
- Erythematous, pruritic, and serpinous plaques (feet, back, buttocks, thighs, or abdomen).
- Eruptions might be secondarily infected.
- Diagnosis: clinical.
- Condition is self-limiting:
 - Larvae are unable to penetrate the basement membrane and invade the dermis in humans.
- Treatment: albendazol, ivermectin.







Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling

Gwenan M Knight, C Finn McQuaid, Peter J Dodd*, Rein M G J Houben*

Funding UK Medical Research Council, Bill & Melinda Gates Foundation, and European Research Council.

Lancet Infect Dis 2019;19: 903–12







Background

- To end the global tuberculosis epidemic, latent tuberculosis infection needs to be addressed.
- All standard treatments for latent tuberculosis contain drugs to which multidrug-resistant (MDR) *Mycobacterium tuberculosis* is resistant.
- We aimed to estimate the global burden of multidrugresistant latent tuberculosis infection.







- We estimated national trends in the proportion of new tuberculosis cases that were caused by MDR strains.
 - By fitting a flexible statistical model to tuberculosis drug resistance surveillance and survey data collated by WHO.
- We used these data as a proxy for the proportion of new infections caused by MDR *M tuberculosis*.
 - Multiplied trends in annual risk of infection from previous estimates of the burden of latent tuberculosis to generate trends in the annual risk of infection with MDR MT.
- These estimates were used in a cohort model to estimate changes in the global and national prevalence of latent infection with MDR *MT*.
- We also estimated recent infection levels (2013 and 2014) and made predictions for the future burden of MDR tuberculosis in 2035 and 2050.







Findings

- 19.1 million (95% uncertainty interval [UI] 16.4 million–21.7 million) people were latently infected with MDR tuberculosis in 2014.
 - Global prevalence of 0.3% (95% UI 0.2-0.3).
- MDR strains accounted for 1.2% (95% UI 1.0–1.4) of the total latent tuberculosis burden.
 - 2.9% (95% UI 2.6–3.1) of the burden among children < 15 years (RR < 15 years vs those > 15 years: 2.65 [95% UI 2.11–3.25]).
- Recent latent infection with MDR *M tuberculosis* meant that 1.9 million (95% UI 1.7 million–2.3 million) people globally were at high risk of active MDR tuberculosis in 2015.







Prevalence of latent multidrug-resistant tuberculosis infection, by WHO region.









Estimated worldwide prevalence of latent multidrug-resistant tuberculosis infection.









Prevalence of latent multidrug-resistant tuberculosis infection in each age group.



European



South-East Asia



Consejería de Sanidad





Eastern Mediterranean



Western Pacific





Interpretation

- We estimate:
 - 3/1000 people globally carry latent MDR tuberculosis infection.
 - Prevalence is around ten times higher among those younger than 15 years.
- If current trends continue...
 - Proportion of latent tuberculosis caused by MDR strains will increase.
 - Will pose serious challenges for management of latent tuberculosis—a cornerstone of tuberculosis elimination strategies.







The burden of latent multidrug-resistant tuberculosis

- 25% of the world's population could have latent tuberculosis infection.
 - 5–10% will develop active disease during their lifetime.
 - 10% annually among people with HIV.
- Failure to implement effective tuberculosis control measures to manage latent infection threatens elimination goals.
 - Groups at high risk of active tuberculosis are the focus of programmatic management of latent tuberculosis infection.
- Latent tuberculosis infection therapy is thought to be ineffective against multidrug-resistant (MDR).
- 19 million people could be latently infected with MDR tuberculosis (1.2% of the total burden of latent infection).





Garcia-Basteiro AL. Lancet Infect Dis. 2019 Jul 22;19(8):802–3.



The burden of latent multidrug-resistant tuberculosis

- Children < 15 years, had more than double the risk of latent MDR tuberculosis infection that adults.
 - Transmission of MDR strains of tuberculosis is worryingly high and probably increasing, and should be urgently addressed.
 - Even if all tuberculosis transmission was halted, reactivation of latent infections would mean that the future burden of MDR disease would still be substantial.
- Latent MDR tuberculosis infection will continue to rise if MDR tuberculosis transmission rates persist.
 - An increasing proportion of people with latent infections might not benefit from recommended tuberculosis preventive therapy regimens.
- Strengthen epidemiological surveillance of MDR tuberculosis and programmatic management of active and latent infections to reduce transmission of MDR tuberculosis.
- Only 25% of people with active MDR tuberculosis are detected.
 - Compared with 64% of people with all types of tuberculosis in 2017.
- Universal tuberculosis preventive therapy would be of great relevance in settings with a high prevalence of MDR tuberculosis.

Garcia-Basteiro AL. Lancet Infect Dis. 2019 Jul 22;19(8):802–3.







Case record

- 46-year-old man.
- Relapsed B-cell acute lymphoblastic leukaemia...
 - Allogeneic haematopoietic stem cell transplantation.
 - 4 months previously: CD19
 CAR T-cell therapy.
- Limb weakness, imbalance, cognitive impairment, and seizures.
- Underlying leukaemia: low minimal residual disease.

Marzolini MAV. Lancet Infect Dis. 2019 Jul;19(7):788.









Case record



https://www.pathpedia.com/education/eatlas/histopathology/ brain_and_cord/cns_toxoplasmosis.aspx





- Brain biopsy:
 - Toxoplasma gondii tachyzoites.
- PCR CSF: Toxoplasma.
- Pyrimethamine, sulfadiazine and folinic acid.

Marzolini MAV. Lancet Infect Dis. 2019 Jul;19(7):788.



Brain toxoplasmosis

- Neurotoxicity following CD19 CAR-T cell therapy:
 - Encephalopathy syndrome ± seizures.
- Patient was Toxoplasma (IgG) seropositive, whereas his donor was seronegative.
 - Azithromycin prophylaxis.







CAR T-cell Therapy



Chlorhexidine for meatal cleaning in reducing catheterassociated urinary tract infections: a multicentre steppedwedge randomised controlled trial

Oyebola Fasugba, Allen C Cheng, Victoria Gregory, Nicholas Graves, Jane Koerner, Peter Collignon, Anne Gardner, Brett G Mitchell

Funding: HCF Research Foundation.

Fasugba O, Lancet Infect Dis. 2019 Jun;19(6):611-9.






Background

- Benefits of antiseptic meatal cleaning in reducing catheterassociated urinary tract infection (UTI) is inconclusive.
- We assessed the efficacy of 0.1% chlorhexidine solution compared with normal saline for meatal cleaning before urinary catheter insertion
 - In reducing the incidence of catheter-associated asymptomatic bacteriuria and UTI.







Methods

- A cross-sectional, stepped-wedge, open-label, randomised controlled trial.
- Eligible hospitals:
 - Australian public and private hospitals, with an intensive care unit and more than 30.000 hospital admissions per year.
- Hospitals were randomly assigned to an intervention crossover date (computer-generated randomisation system).
 - Crossover dates occurred every 8 weeks.
 - During the first 8 weeks of the study, no hospitals were exposed to the intervention (control phase), after which each hospital sequentially crossed over from the control to the intervention every 8 weeks.
- Patients were included: requiring a urinary catheter.







Methods 2

- Participants were excluded...
 - < 2 years,</p>
 - Medical reason preventing the use of the chlorhexidine.
 - Catheter inserted in theatre, did not have the catheter insertion date documented, required in-andout or suprapubic catheterisation,.
 - Symptoms and signs suggestive of UTI at the time of catheter insertion.
 - Currently undergoing treatment for UTI.
- Intervention: before urinary catheterisation, meatal cleaning...
 - 0.1% chlorhexidine solution for
 - 0.9% normal saline used in the control phase.
- Masking of hospitals was not possible.
 - It was not feasible to mask staff administering the intervention.
- Co-primary outcomes:
 - N^a of cases of catheter-associated asymptomatic bacteriuria and UTI per 100 catheterdays.
 - Assessed within 7 days of catheter insertion in the intention-to-treat population.
- Australian New Zealand Clinical Trials Registry: ACTRN12617000373370.









	Total (n=1642)	Control period				Intervention period			
		Hospital A (n=53)	Hospital B (n=130)	Hospital C (n=514)	Total control (n=697)	Hospital A (n=637)	Hospital B (n=127)	Hospital C (n=181)	Total intervention (n=945)
Median age, years (IQR)	69 (38-82)	79 (68-86)	72 (64-81)	80 (70-88)	78 (69-87)	35 (30-56)	73 (60-84)	82 (70-89)	50 (32-76)
Sex									
Female	949 (58%)	27 (51%)	52 (40%)	250 (49%)	329 (47%)	477 (75%)	65 (51%)	78 (43%)	620 (66%)
Male	693 (42%)	26 (49%)	78 (60%)	264 (51%)	368 (53%)	160 (25%)	62 (49%)	103 (57%)	325 (34%)
Comorbidities									
Cancer	327 (20%)	9 (17%)	32 (25%)	160 (31%)	201 (29%)	42 (7%)	24 (19%)	60 (33%)	126 (13%)
Diabetes	229 (14%)	2 (4%)	34 (26%)	89 (17%)	125 (18%)	43 (7%)	29 (23%)	32 (18%)	104 (11%)
Liver disease	63 (4%)	2 (4%)	9 (7%)	29 (6%)	40 (6%)	10 (2%)	6 (5%)	7 (4%)	20 (2%)
Data are median (I	QR) orn (%).								

Table 1: Baseline characteristics by study period and hospital







Findings

- 21 hospitals were assessed for eligibility.
 - Three were successfully enrolled and randomised.
- 1642 participants were included in the study (Aug 1, 2017, and March 12, 2018)
- Control period: 697 patients (42%)
 - 0.45 catheter-associated UTI cases and 1.00 catheter-associated asymptomatic bacteriuria cases / 100 catheter-days.
- Intervention period: 945 patients (58%)
 - 0.17 catheter-associated UTI cases and 0.68 catheter-associated asymptomatic bacteriuria cases / 100 catheter-days.







Findings

- The intervention was associated:
 - 74% reduction in the incidence of catheter-associated asymptomatic bacteriuria
 - IRR 0.26, 95% CI 0.08–0.86, p=0.026.
 - 94% decrease in the incidence of catheter-associated UTI
 - IRR 0.06, 95% CI 0.01–0.32, p=0.00080.
- There were no reported adverse events.







	Control period			Intervention period			Poisson regression	
	Number of patients	Catheter days	Number (incidence*)	Number of patients	Catheter days	Number (incidence*)	IRR (95% CI)	pvalue
CA-ASB								
Hospital A	53	254	8 (3-15)	637	1327	11 (0-82)	1 (reference)	tt:
Hospital B	130	552	5 (0-91)	127	418	2 (0-48)	0-35 (0-12-1-03)	0-056
Hospital C	514	2093	16 (0-76)	181	593	3 (0-49)	0-27 (0-09-0-78)	0-015
Total	697	2889	29 (1-00)	945	2338	16 (0-68)	**	99
CAUTI								
Hospital A	53	236	3 (1-18)	637	1345	4 (0-30)	1 (reference)	23
Hospital B	130	552	2 (0-36)	127	418	0 (0-00)	0.17 (0.04-0.73)	0-018
Hospital C	514	2068	8 (0-38)	181	618	0 (0-00)	0.14 (0.04-0.51)	0-0026
Total	697	2856	13 (0-45)	945	2381	4 (0-17)		17.1

There were no cases of the secondary outcome (bloodstream infections secondary to a urinary tract infection) in any hospital in either group of the study. CA-ASB- catheter-associated asymptomatic bacteriuria. CAUTI-catheter-associated urinary tract infection. IRR-incidence rate ratio. *per 100 catheter days.

Table 2: Number and incidence of CA-ASB and CAUTI, stratified by study period and hospital







Incidence of catheter-associated asymptomatic bacteriuria during intervention and control periods, stratified by hospital.





Incidence of CAUTI during control and intervention periods, stratified by hospital.







Interpretation

- Chlorhexidine for meatal cleaning before catheter insertion...







Non-antibiotic prevention strategies against catheter-associated urinary tract infections

- This study gives important evidence for the use of chlorhexidine solution for cleaning of the urethral meatus before catheter insertion to decrease the incidence of catheter-assisted UTI...
- But timely removal remains as another prevention strategy.

Laan BJ. Lancet Infect Dis. 2019 May 20;19(6):562-4.







Maculopapular rash after interleukin 6 inhibitor therapy in a patient with rheumatoid arthritis.



- A 62-year-old woman with severe rheumatoid arthritis
 - Tocilizumab , prednisone (5 mg/ day) and methotrexate.
- Multiple polymorphic, partly raised, confluent, erythematous non-pruritic maculopapular rash
 - Central clearing over her back, abdomen, arms, and legs, including palms and soles.
- Progressively worsening tingling and numbness in her hands and feet.





Puja H Nambiar et al. Lancet Infect Dis 2019; 19: 787.



Leprosy after interleukin 6 inhibitor therapy in a patient with rheumatoid arthritis.

- Skin biopsy:
 - Granulomatous
 inflammatory infiltrate
 involvement of
 cutaneous nerves.
 - Fite's stain:
 tuberculoid
 leprosy.

Puja H Nambiar et al. *Lancet Infect Dis* 2019; 19: 787.







https://laboratoryinfo.com/wade-fite-staining-technique-for-mycobacterium-leprae/



Maculopapular rash after interleukin 6 inhibitor therapy in a patient with rheumatoid arthritis.

- Tocilizumab, methotrexate, and prednisone were discontinued.
- Rifampicin 600 mg + dapsone 100 mg/ daily.
- The rash resolved after 6 months of therapy.
 - Patient continued to have progressive paraesthesia from sensorimotor polyneuropathy: neuropathic ulcers requiring aggressive wound care.
- After remission for 4 years she developed recurrence of rash.
 - A biopsy of the rash confirmed type 1 reversal reaction.
 - Oral prednisone tapered over 6 months.
- 4 years later, she has no symptoms except for persistent numbness and tingling in her hands and feet.





Puja H Nambiar et al. Lancet Infect Dis 2019; 19: 787.



Leprosy after interleukin 6 inhibitor therapy in a patient with rheumatoid arthritis.

- She had never travelled outside the USA, had contact with people with leprosy, or had any contact with armadillos.
- An association exists between leprosy and TNF inhibitor therapy.
 - This is the first case, of leprosy after use of an IL-6 inhibitor.
- Incidental contact with armadillos might also play a role in the transmission of leprosy.





Puja H Nambiar et al. Lancet Infect Dis 2019; 19: 787.



Mimicking oesophageal cancer

- 75-year-old woman. Active smoker.
- Rapid progressive dysphagia, odynophagia, regurgitations, and weight loss.
- High-resolution manometry: type 2 achalasia.
- Oral endoscopic myotomy:
 - Underlying neoplastic lesion was suspected.
- Endoscopic ultrasonography:
 - Suggested a neoplastic lesion of 28×17 mm, extending into the muscularis mucosae; staged uT3N0.





Deswysen Y. Lancet Infect Dis. 2019 May;19(5):558.



Mimicking oesophageal cancer

- 18 Fluorodeoxyglucose PET/CT
 - Intense focal uptake at the level of the oesophageal lesion.
- CT scan:
 - Asymmetric thickening of the cardia + enlarged lymph nodes near the oesophagus ¿Neoplasia?
- Laparoscopic exploration and jejunostomy.
 - No liquid or tumoural signs were noted.

Deswysen Y. Lancet Infect Dis. 2019 May;19(5):558.







Mimicking oesophageal cancer

- New biopsies by endoscopy :
 - Numerous branching filamentous organisms invading inflammatory tissue: actinomycosis.
- Culturing of Gram-positive anaerobic bacteria and MALDI-TOF
 - Actinomyces odontolyticus.
- Amoxicillin.
 - Progressive resolution of symptoms after 3 months.





Deswysen Y. Lancet Infect Dis. 2019 May;19(5):558.

