# Vitamine D et infections

## Faut-il prescrire de la vitamine D pour prévenir et traiter les infections ?

Journée SRO - 8 octobre 2022

Pr Vincent Dubée

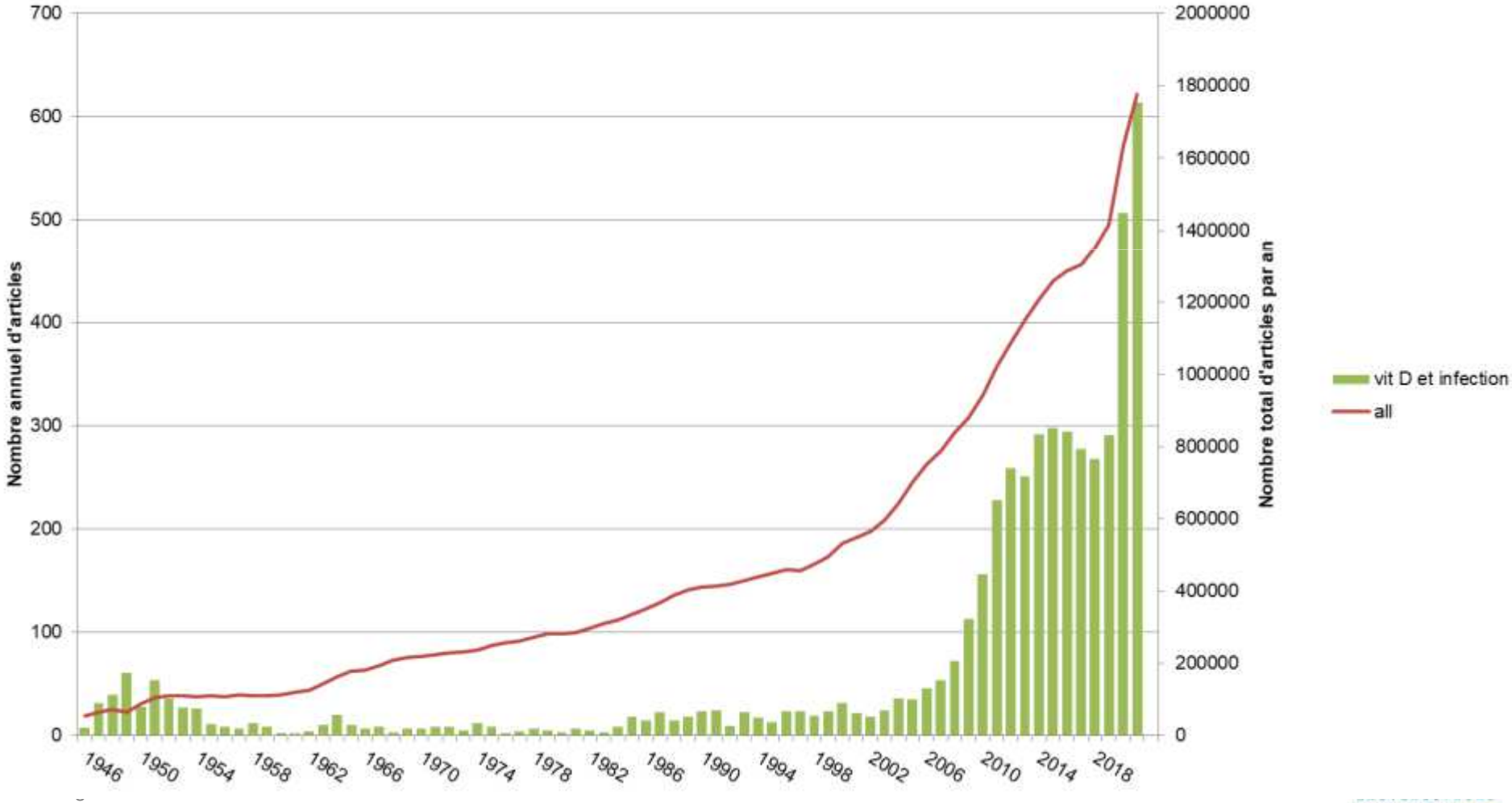
Service des maladies infectieuses et tropicales

CHU ANGERS
CENTRE HOSPITALIER UNIVERSITAIRE

# Lien d'intérêt

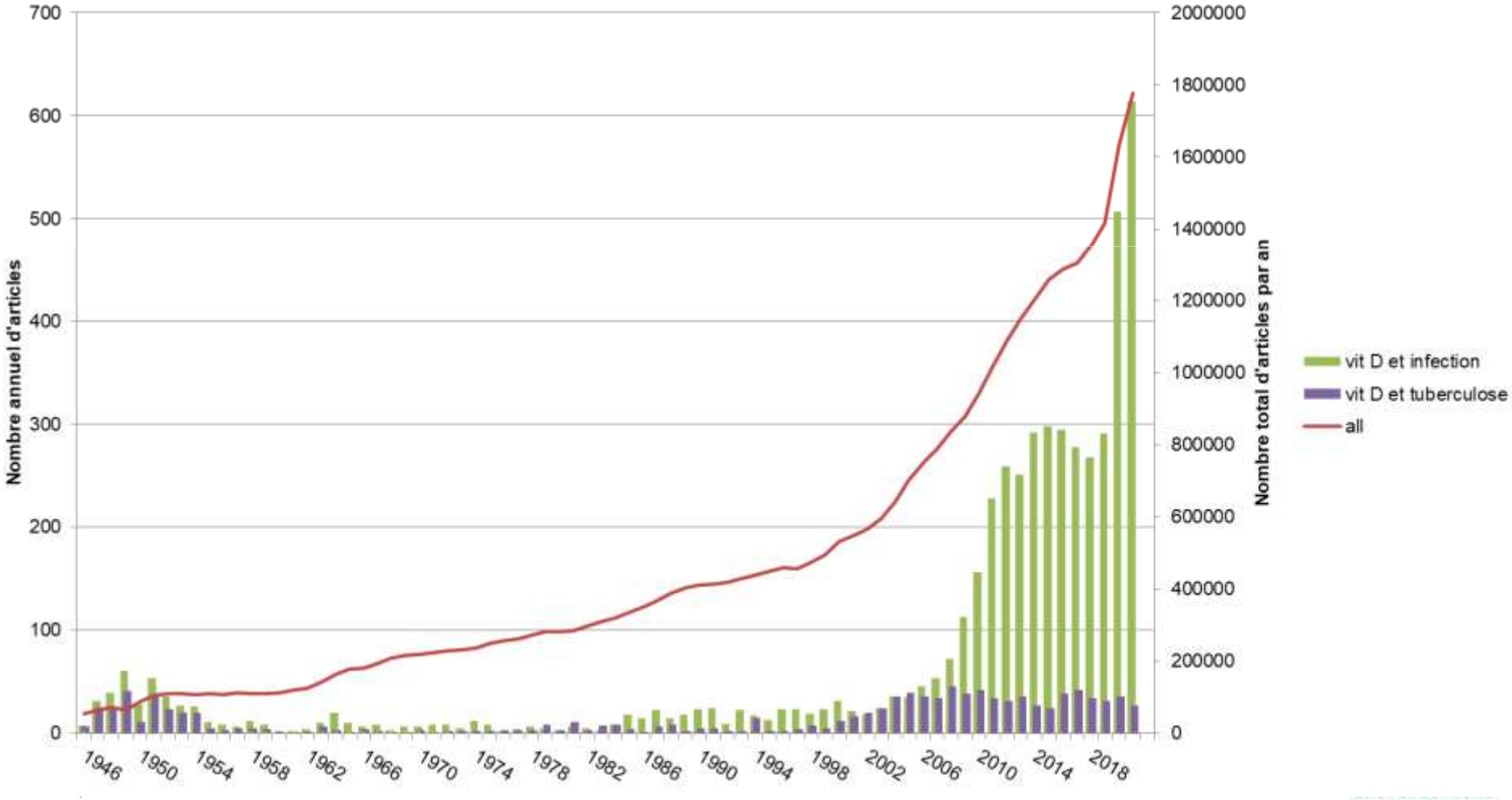
- Pas de lien d'intérêt en rapport avec la présentation

# Un sujet très exploré



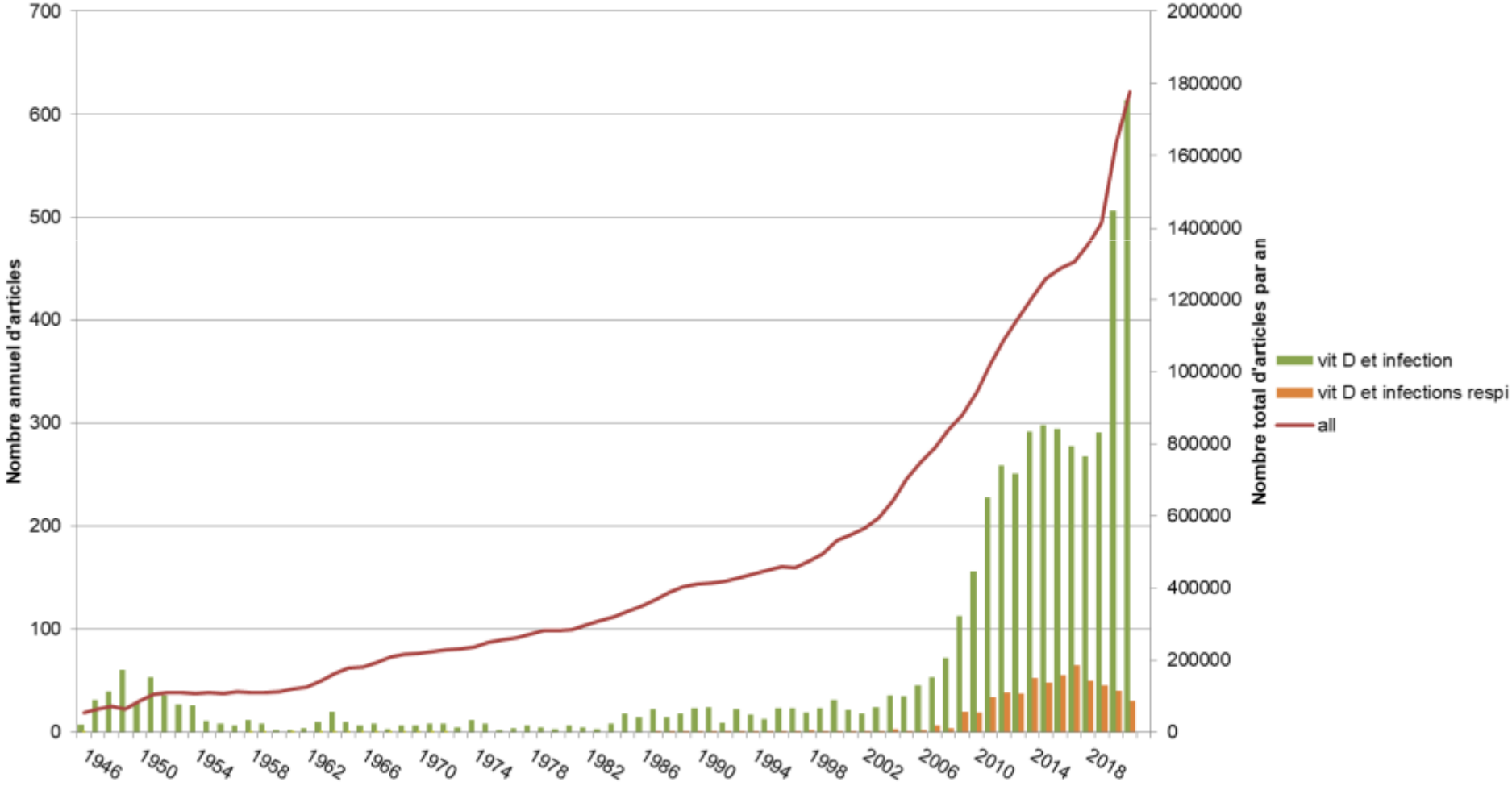
# Un sujet très exploré

## La mode de la tuberculose



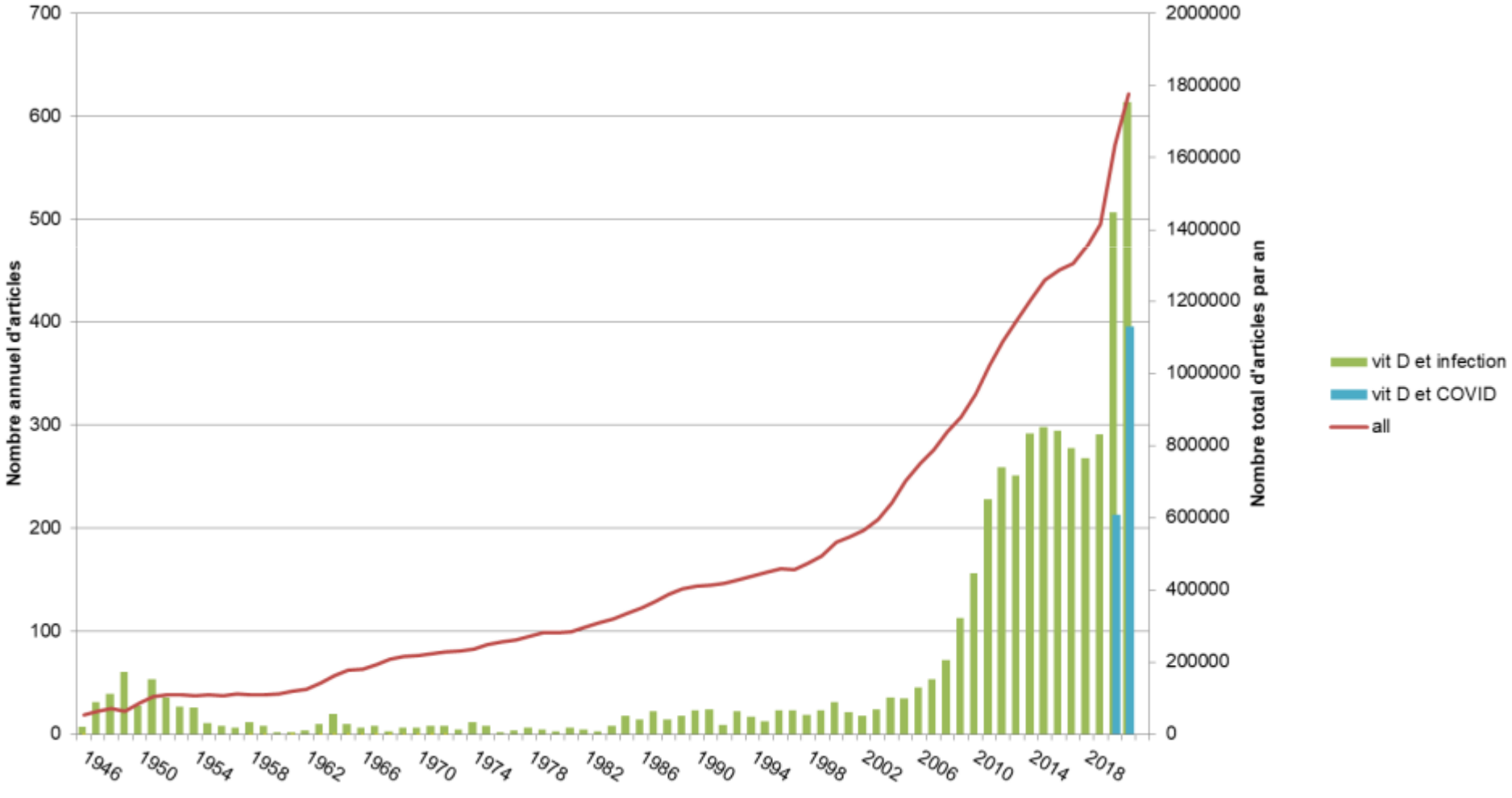
# Un sujet très exploré

## Les infections respiratoires (hors COVID-19)



# Un sujet très exploré

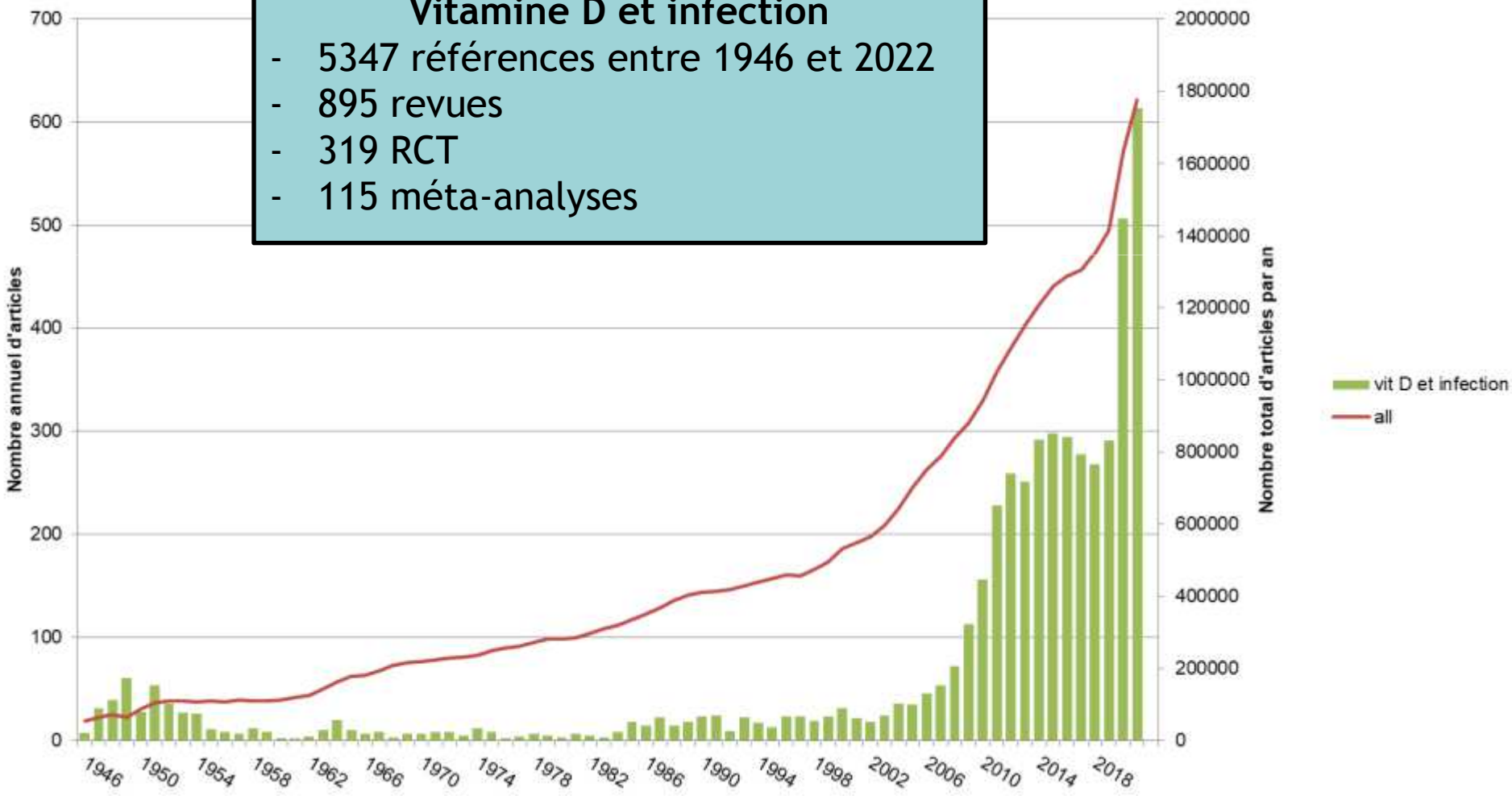
## COVID-19 et vitamine D



# Un sujet très exploré

**Vitamine D et infection**

- 5347 références entre 1946 et 2022
- 895 revues
- 319 RCT
- 115 méta-analyses



# Lien établi entre concentration entre vitamine D et mortalité

| | No of studies | No of participants | No of deaths | Relative risk (95% CI)* for cause specific mortality |
|---|---|---|---|---|
| **Cardiovascular death** | | | | |
| Primary prevention cohorts | 19 | 80 662 | 6416 | 1.35 (1.13 to 1.61) |
| Secondary prevention cohorts | 10 | 20 987 | 3787 | 1.60 (1.32 to 1.94) |
| All cohorts | 29 | 101 649 | 10 203 | 1.43 (1.25 to 1.64) |
| **Cancer death** | | | | |
| Primary prevention cohorts | 12 | 104 353 | 5003 | 1.14 (1.01 to 1.29) |
| Secondary prevention cohorts | 5 | 16 382 | 1617 | 1.59 (1.17 to 2.16) |
| All cohorts | 17 | 120 735 | 6620 | 1.25 (1.10 to 1.43) |
| **Non-cardiovascular, non-cancer death** | | | | |
| Primary prevention cohorts | 7 | 38 526 | 1444 | 1.30 (1.07 to 1.59) |
| Secondary prevention cohorts | 3 | 13 035 | 1121 | 1.49 (0.94 to 2.35) |
| All cohorts | 10 | 51 561 | 2565 | 1.34 (1.13 to 1.60) |
| **All cause mortality** | | | | |
| Primary prevention cohorts | 27 | 780 990 | 48 488 | 1.35 (1.22 to 1.49) |
| Secondary prevention cohorts | 41 | 59 918 | 16 148 | 1.50 (1.36 to 1.65) |
| All cohorts | 68 | 840 908 | 64 636 | 1.44 (1.34 to 1.55) |

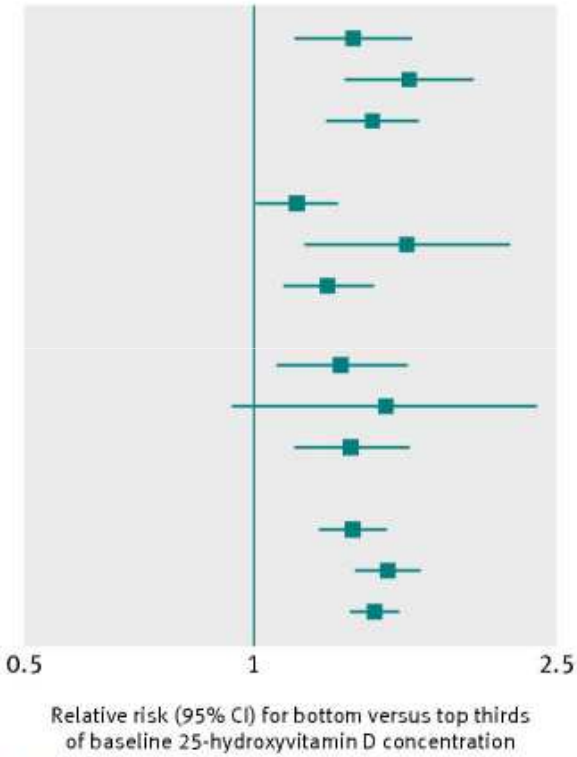



**Fig 1** Association of circulating 25-hydroxyvitamin D concentrations with cause specific mortality in observational cohort studies. *Pooled estimates are based on random effects meta-analysis. Using fixed effects models, for primary prevention cohorts, secondary prevention cohorts, and all cohorts, the estimates were 1.40 (1.32 to 1.47), 1.50 (1.35 to 1.66), and 1.42 (1.35 to 1.49) for cardiovascular deaths; 1.10 (1.02 to 1.17), 1.45 (1.28 to 1.65), and 1.16 (1.10 to 1.24) for cancer deaths; 1.28 (1.12 to 1.47), 1.38 (1.09 to 1.75), and 1.30 (1.16 to 1.47) for non-vascular, non-cancer deaths; and 1.45 (1.41 to 1.49), 1.49 (1.42 to 1.56), and 1.44 (1.40 to 1.47) for all cause deaths. Size of data marker is proportional to inverse of variance of relative risk; horizontal line represents 95% CI. Corresponding forest plots and $I^2$ (95% CI) estimates are provided in supplementary material

Chowdury R et al, BMJ 2014

# Vitamine D et infections - Rationnel

- La carence en vitamine D touche 40 à 60% de la population européenne en bonne santé

- Carence en vitamine D associée à un moins bon pronostic chez les patients atteints de :
  - → Tuberculose
  - → VIH
  - → Pneumopathie aiguë communautaire
  - → Sepsis/choc septique
  - → …

# Vitamine D et infections - Rationnel

- La supplémentation en vitamine D en population générale diminuerait la mortalité toutes causes (Autiers et al, Arch Intern Med 2007)

- **Quel est l'effet de la supplémentation en vitamine D sur le risque d'infection et sur l'évolution des infections ?**

# Physiopathologie

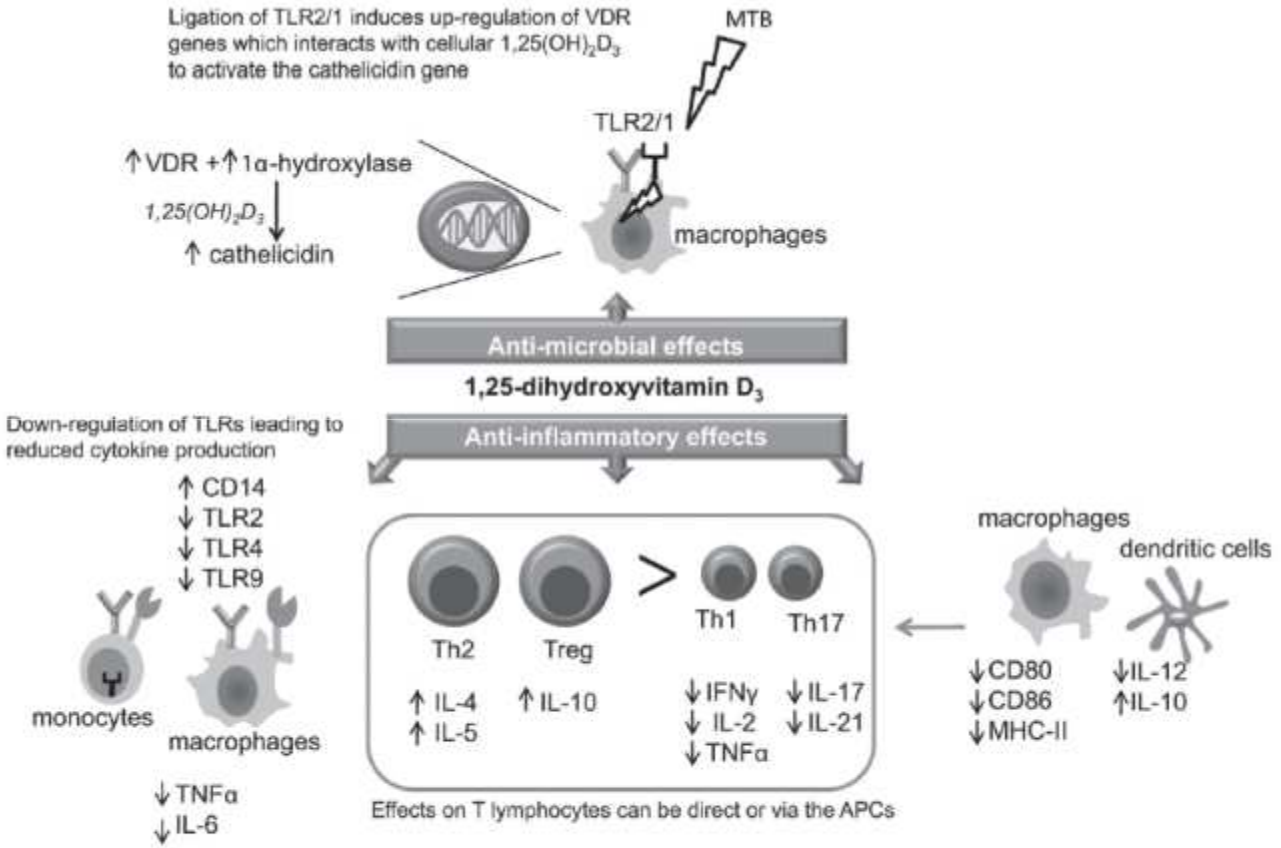



Figure 2. An overview of the anti-microbial and anti-inflammatory effects of vitamin $D_3$. Vitamin $D_3$ can influence the differentiation of naïve $CD4^+$ lymphocytes directly and indirectly via the antigen-presenting cells (APC). Overall, it favors a Thelper (Th)2 and regulatory T cell (Treg) cytokine profile over an anti-inflammatory Th1 and Th17 phenotype. Down-regulation of toll-like receptor (TLR) 2, TLR4 and TLR9 on human monocytes/macrophages by vitamin $D_3$ also leads to repression of anti-inflammatory cytokines. The anti-microbial effect of vitamin $D_3$ upon MTB stimulation is triggered when activation of TLR2/1 causes an up-regulation of both vitamin D receptor (VDR) and 1α-hydroxylase genes. The consequential increased in local production of $1,25(OH)_2D_3$ interact with the up-regulated VDR and in turn activated cathelicidin gene and an increased synthesis of cathelicidin, an anti-microbial peptide.

Leng Khoo A et al, Critical Reviews in Microbiology 2012

# Complexité de la question

- Intervention
  - → Forme de vitamine D ($D_2$/$D_3$)
  - → Dose de vitamine D
  - → Rythme d'administration (bolus/quotidienne)

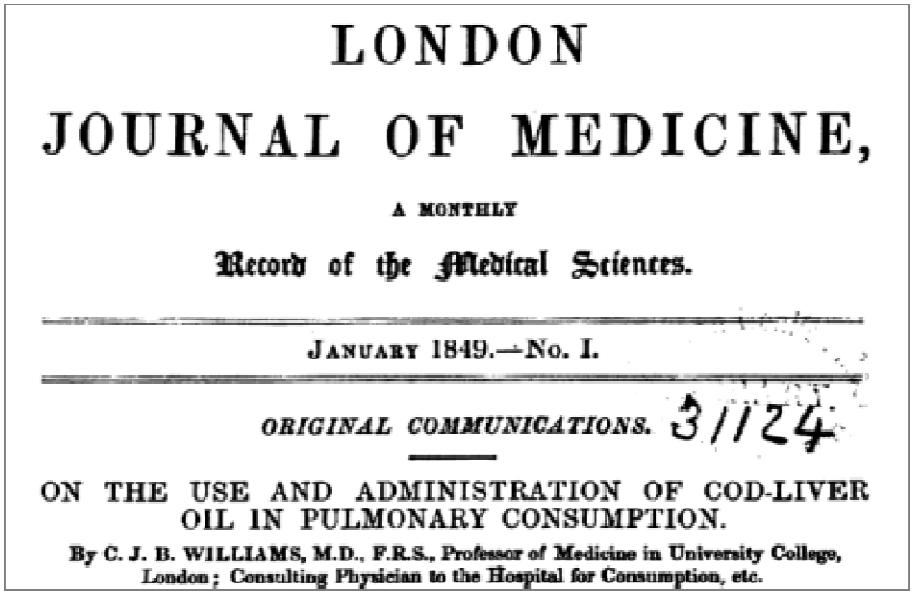
- Population
  - → Carence en vitamine D O/N
  - → Etat nutritionnel global
  - → Enfants/adultes

- Condition
  - → Infections bactériennes
  - → Mycobactéries
  - → Infections virales
  - → Infections respiratoires

# VITAMINE D ET TUBERCULOSE

# Une vieille histoire

- 1849 : “the pure fresh oil from the liver of the cod is more beneficial in the treatment of pulmonary consumption than any agent, medicinal, dietetic, or regiminal, that has yet been employed”



LONDON

JOURNAL OF MEDICINE,

A MONTHLY

Record of the Medical Sciences.

JANUARY 1849.—No. I.

ORIGINAL COMMUNICATIONS. 3/124

ON THE USE AND ADMINISTRATION OF COD-LIVER OIL IN PULMONARY CONSUMPTION.

By C. J. B. WILLIAMS, M.D., F.R.S., Professor of Medicine in University College, London; Consulting Physician to the Hospital for Consumption, etc.

- Isolement de la vitamin D3 de l’huile de foie de morue
- Utilisation standardisée de la vitamin D PO pour le traitement de la tuberculose cutanée (Charpy, 1950)

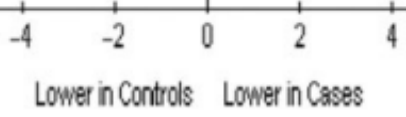
# Vitamine D et tuberculose - rationnel

- Carence en vitamine D plus fréquente chez les sujets atteints de tuberculose

**Table 4** Effect sizes of low serum vitamin D in tuberculosis patients and controls

| Study or sub-category | Cases N | Control N | Effect Size (SE) | Weight % | Effect Size (random) 95% CI |
|---|---|---|---|---|---|
| Davies, UK | 40 | 40 | 0.8600 (0.2300) | 16.69 | 0.86 [0.41, 1.31] |
| Grange, Indonesia | 40 | 38 | 0.1800 (0.2300) | 16.69 | 0.18 [−0.27, 0.63] |
| Davies, Kenya | 15 | 15 | 1.0400 (0.3900) | 8.34 | 1.04 [0.28, 1.80] |
| Davies, Thailand | 51 | 51 | 0.9600 (0.2100) | 18.31 | 0.96 [0.55, 1.37] |
| Chan, Hong Kong | 24 | 24 | 0.3300 (0.3000) | 12.14 | 0.33 [−0.26, 0.92] |
| Wilkinson, UK | 103 | 42 | 0.5900 (0.2300) | 16.69 | 0.59 [0.14, 1.04] |
| Sasidharan, India | 35 | 16 | 0.9400 (0.3200) | 11.13 | 0.94 [0.31, 1.57] |
| Total (95% CI) | 308 | 226 | | 100.00 | 0.68 [0.43, 0.93] |

Test for heterogeneity: $Chi^2 = 10.14$, df = 6 (P = 0.12), $I^2 = 40.8\%$
Test for overall effect: Z = 5.28 (P < 0.00001)






Nnoaham KE & Clarke A, International Journal of Epidemiology 2008

# Rationnel

Augmentation de l'activité anti-mycobactérie in vitro du sérum de sujets traités par vitamine D

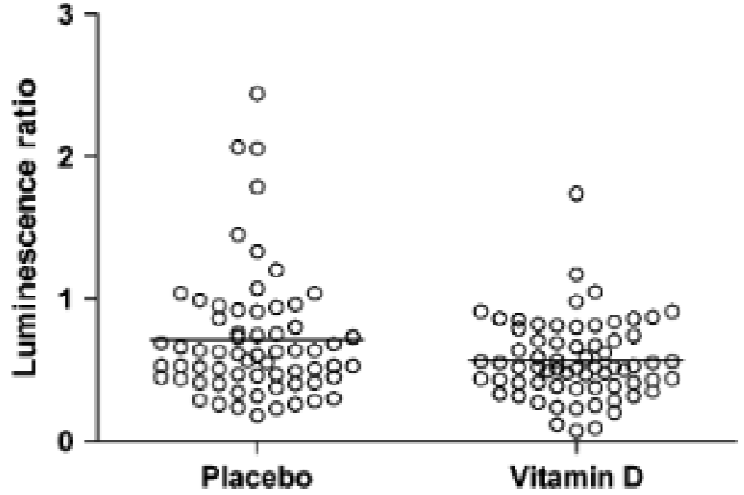



*Figure 2.* Influence of vitamin D supplementation on BCG-lux assay luminescence ratio. Mean BCG-lux assay 24-hour luminescence ratio at follow-up was 20% lower for individuals allocated to vitamin D compared with those allocated to placebo (0.57 vs. 0.71, respectively; 95% confidence interval for difference, 0.01 to 0.25; p = 0.03).

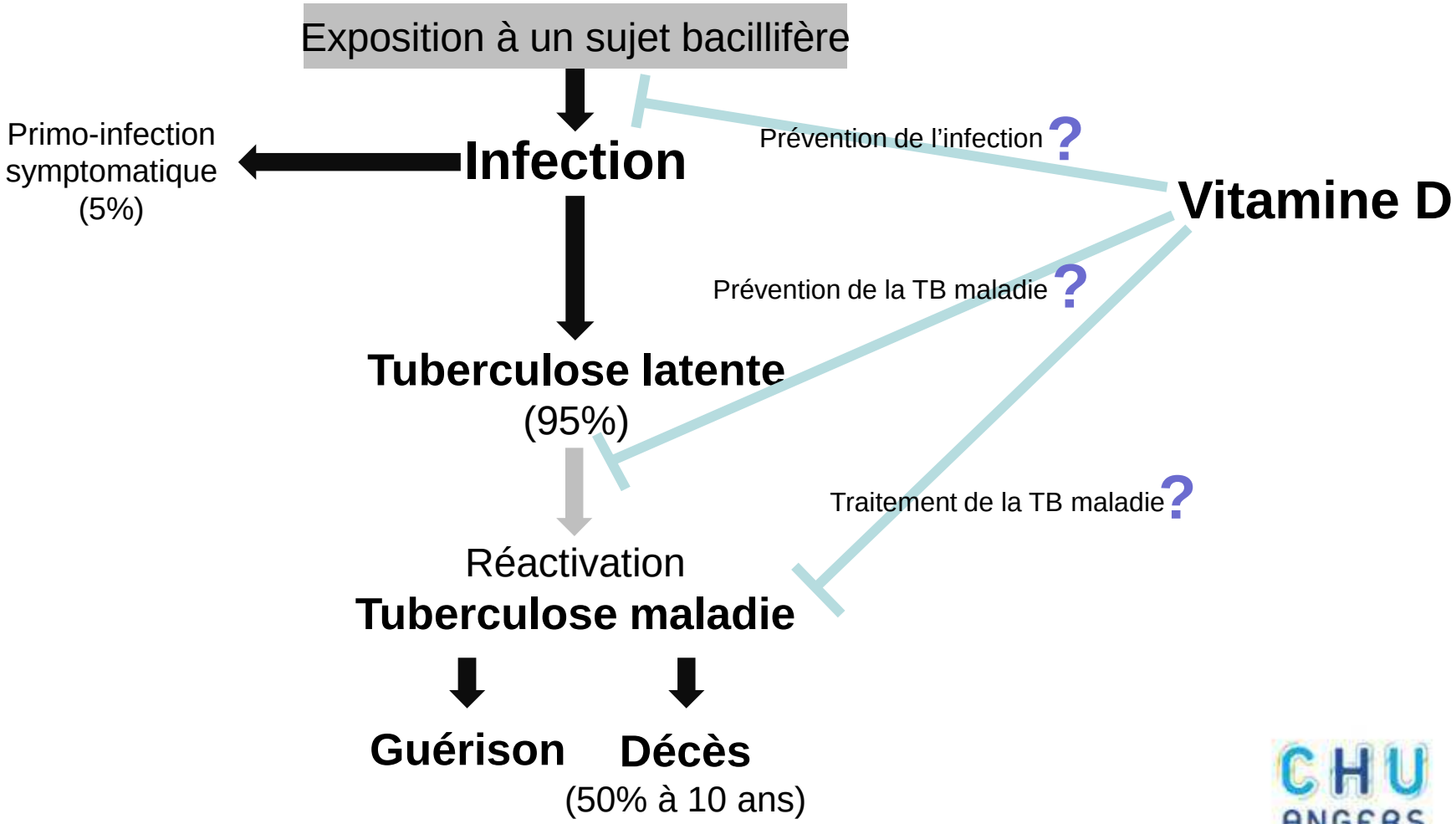
***Mode d'action***

Augmentation du stress oxydatif

Augmentation de la synthèse de cathelicidine

Martineau AR et al, AJRCCM 2007

# Différentes interventions possibles



# Prévention de la tuberculose

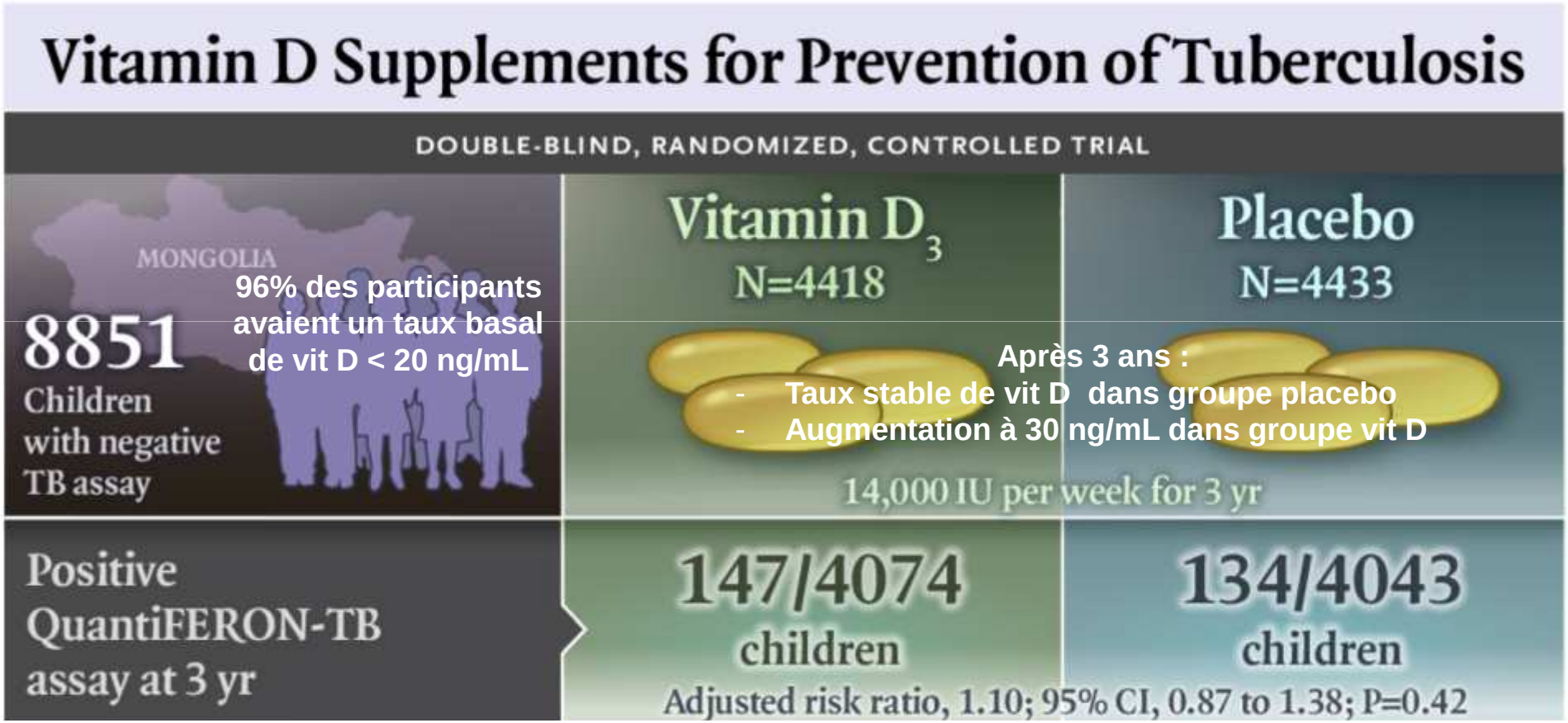
The NEW ENGLAND JOURNAL of MEDICINE

## Vitamin D Supplements for Prevention of Tuberculosis


Ganmaa D *et al.* NEJM 2020

# Prévention de la tuberculose

The NEW ENGLAND JOURNAL of MEDICINE




Ganmaa D *et al.* NEJM 2020

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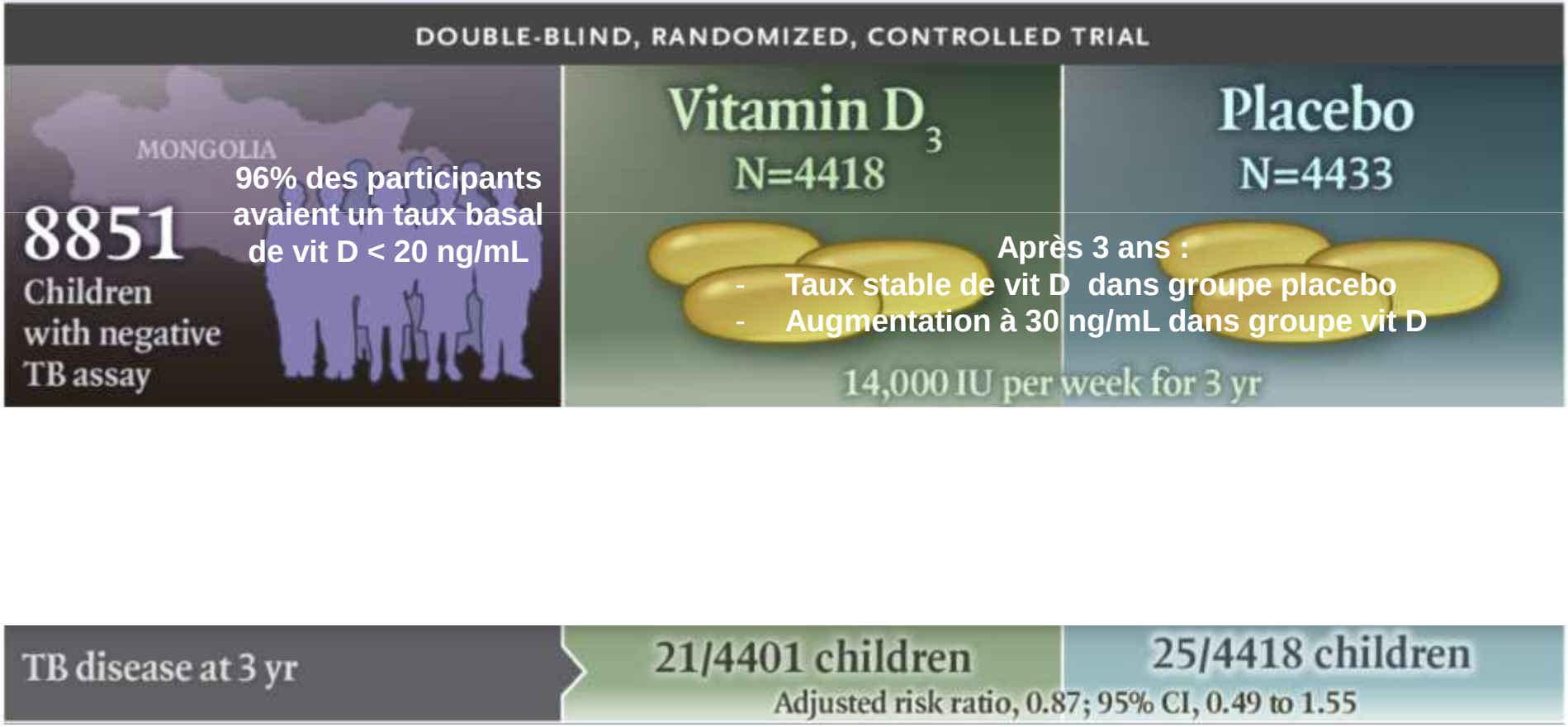
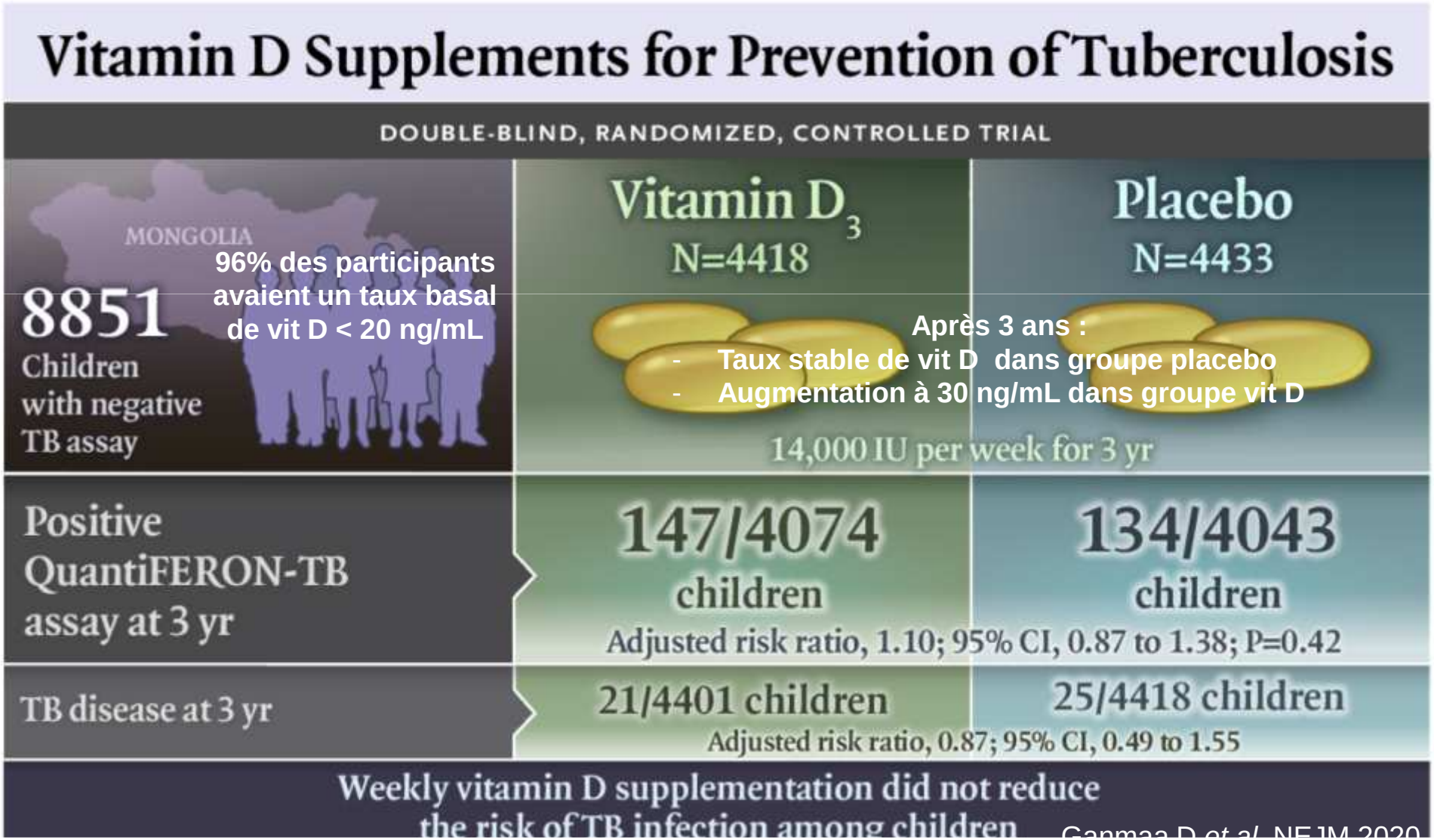
## Vitamin D Supplements for Prevention of Tuberculosis




Ganmaa D *et al.* NEJM 2020

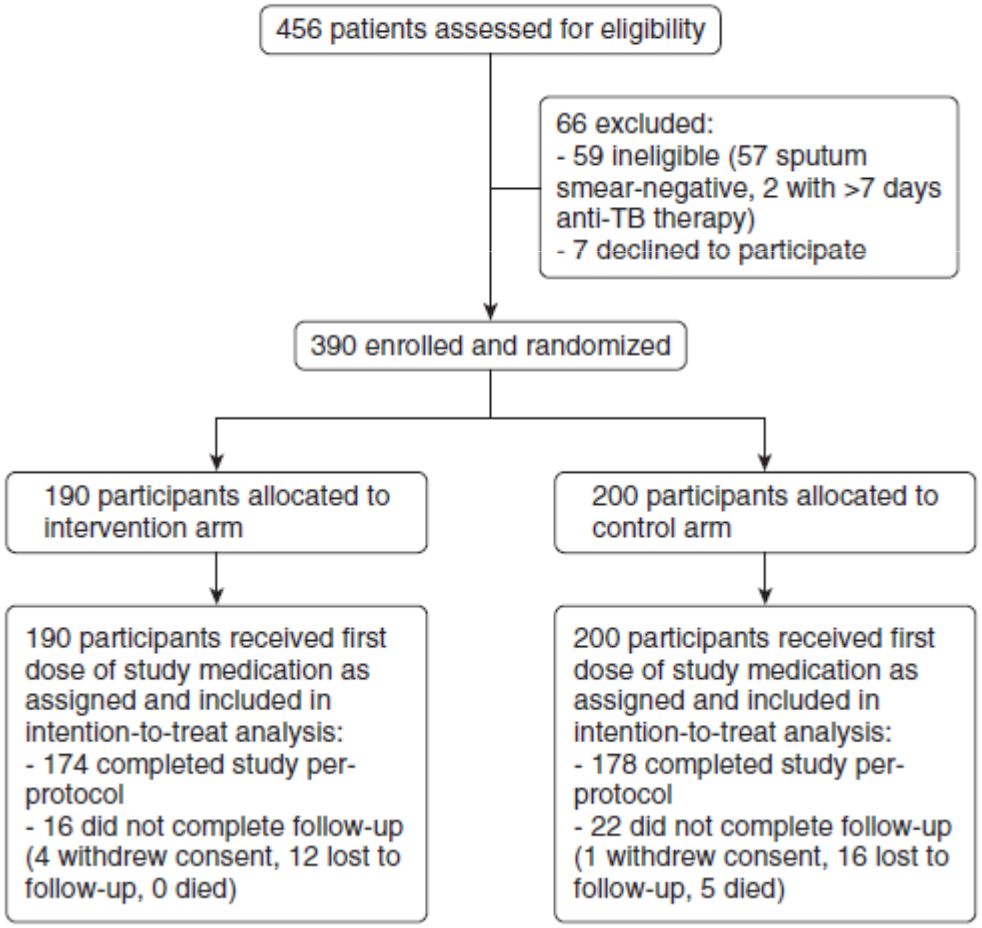
# Prévention de la tuberculose

The NEW ENGLAND JOURNAL of MEDICINE



# Traitement de la tuberculose

- Vitamine D3 dans le traitement de la TB en Mongolie




***Population***
Mongolie
390 adultes atteints de TB maladie BAAR+

***Intervention***
vit D3 140000 UI ou placebo /2 semaines pendant 2 mois
Augmentation nette du taux de vit D dans le groupe intervention

Ganmaa D *et al*, AJRCCM 2017

# Traitement de la tuberculose

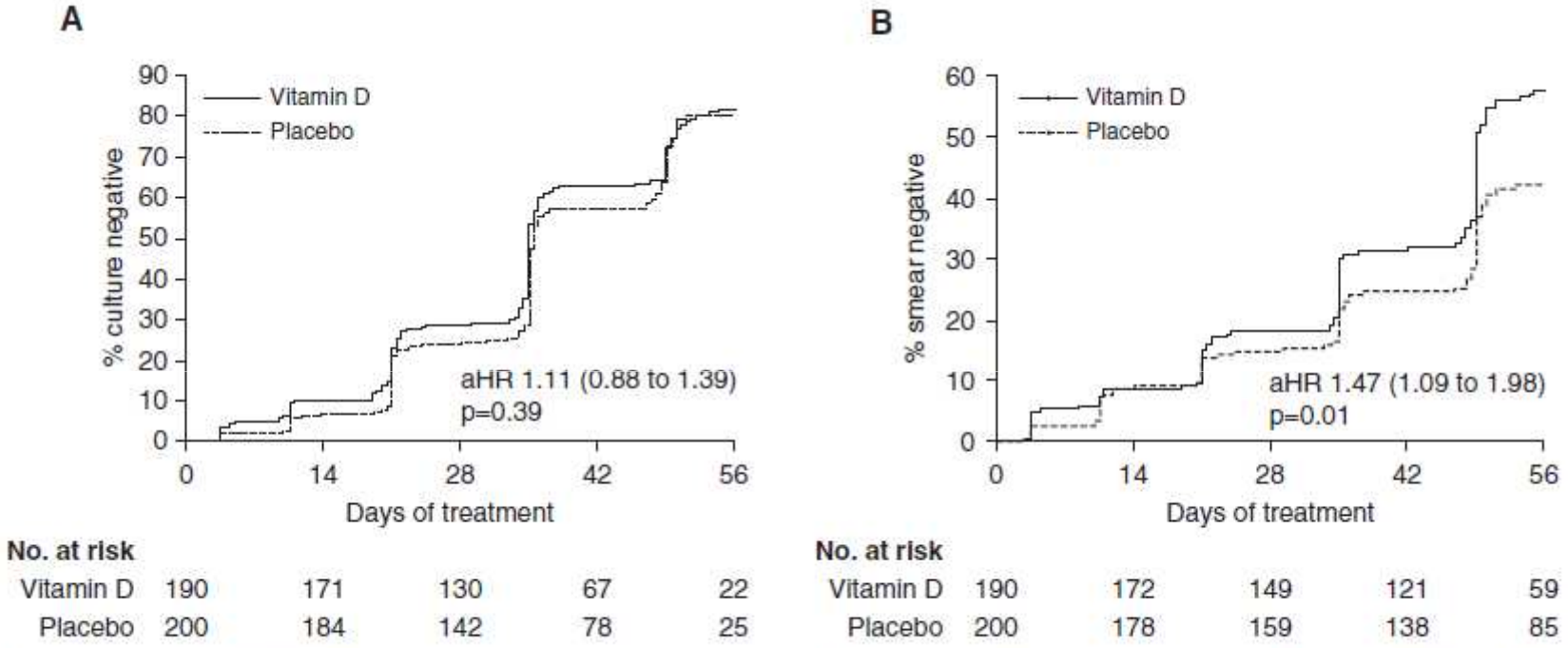



**Figure 2.** Time to sputum culture conversion (*A*) and smear conversion (*B*) by allocation. The number of participants with positive sputum culture/smear remaining in follow-up (number at risk) after 0, 14, 28, 42, and 56 days of antimicrobial therapy is presented. aHR = adjusted hazard ratio.

Pas d'effet significatif sur la vitesse de stérilisation des expectorations
(Accélération significative de la clairance bactérienne chez les patients présentant certains SNP dans les gènes codant pour VDR et CYP27B1)

Ganmaa D *et al*, AJRCCM 2017

# Traitement de la TB – méta-analyse

Méta-analyse des données individuelles – 1850 patients dans 8 études

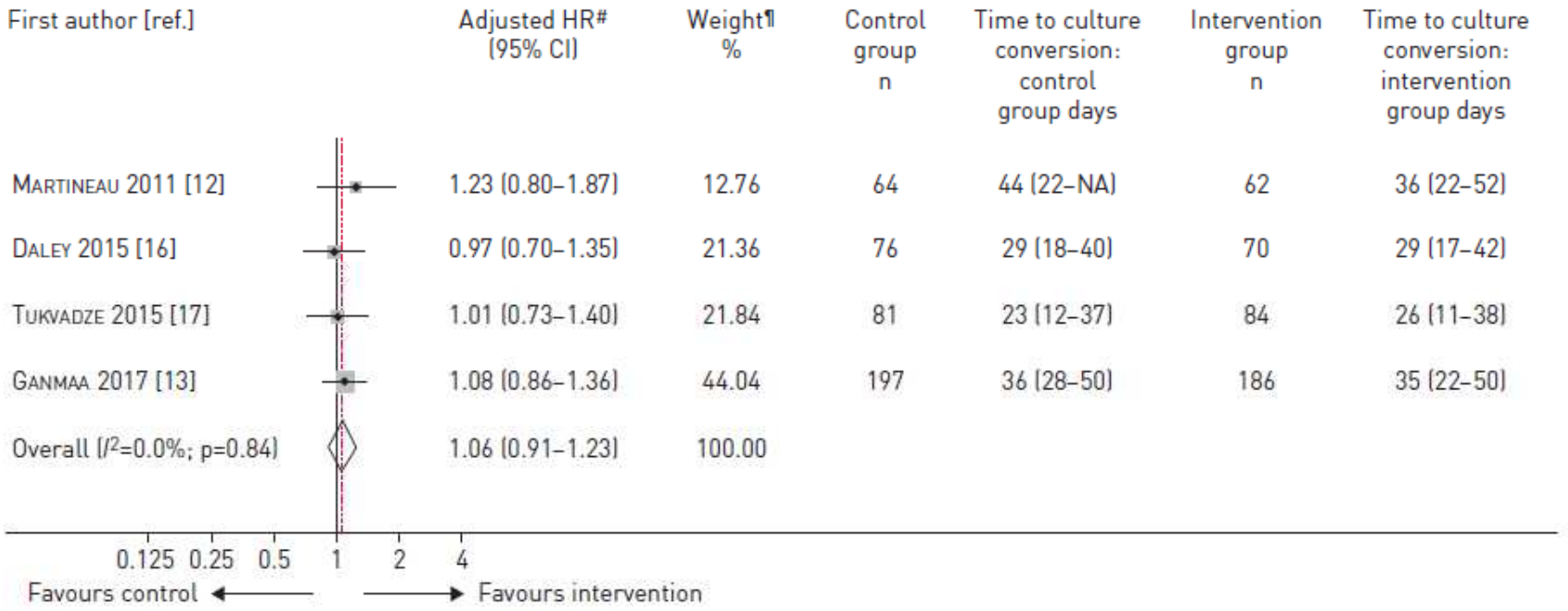



FIGURE 3 Forest plot from two-step individual participant data meta-analysis of adjusted hazard ratios: time to sputum culture conversion by allocation to control (placebo) or intervention (vitamin D). NA: not available, since 75th centiles for time to culture conversion in this group cannot be defined. Data for time to culture conversion are presented as median (interquartile range). #: adjusted for age and sex; ¶: from random effects analysis.

Pas d'effet sur la vitesse de stérilisation des expectorations
TB MDR : stérilisation plus rapide ? 37 patients…

Jolliffe DA et al, Eur Respir J 2019

# En résumé pour la tuberculose

| Affection | Intérêt d'une supplémentation en vitamine D ? |
|---|---|
| Prévention de l'ITL | ✘ |
| Prévention de la TB maladie | ✘ |
| Traitement de la TB maladie | ✘ |

Domaines d'incertitude :

- traitement de la TB multirésistante
- effet sur la rapidité de guérison clinique

# VITAMINE D ET PRÉVENTION DES INFECTIONS RESPIRATOIRES

# Prévention des infections respiratoires

**Table 2. Respiratory Infection.**

| Variable | Vitamin D | Placebo | Adjusted Risk Ratio (95% CI)* |
|---|---|---|---|
| **Acute respiratory infection¶** | | | |
| Participant hospitalized for ≥1 episode — no./total no. (%) | | | |
| Overall | 29/4401 (0.7) | 34/4418 (0.8) | 0.86 (0.52–1.40) |
| Baseline 25(OH)D level <10 ng/ml | 8/1387 (0.6)‖ | 10/1414 (0.7)** | 0.81 (0.32–2.09) |
| Baseline 25(OH)D level ≥10 ng/ml | 21/3013 (0.7)†† | 24/3000 (0.8)‡‡ | 0.86 (0.48–1.55) |
| Participant reported ≥1 episode — no./total no. (%) | | | |
| Overall | 3783/4401 (86.0) | 3793/4418 (85.9) | 1.00 (0.98–1.02) |
| Baseline 25(OH)D level <10 ng/ml | 1195/1387 (86.2) | 1205/1414 (85.2) | 1.01 (0.98–1.04) |
| Baseline 25(OH)D level ≥10 ng/ml | 2587/3013 (85.9) | 2585/3000 (86.2) | 1.00 (0.98–1.02) |
| Participant received ≥1 course of antibiotics for episode — no./total no. (%) | | | |
| Overall | 1272/4401 (28.9) | 1292/4418 (29.3) | 0.99 (0.93–1.05) |
| Baseline 25(OH)D level <10 ng/ml | 392/1387 (28.3) | 399/1414 (28.2) | 0.99 (0.88–1.12) |
| Baseline 25(OH)D level ≥10 ng/ml | 880/3013 (29.2) | 892/3000 (29.7) | 0.98 (0.91–1.06) |



Ganmaa D *et al*, NEJM 2020

# Prévention des infections respiratoires

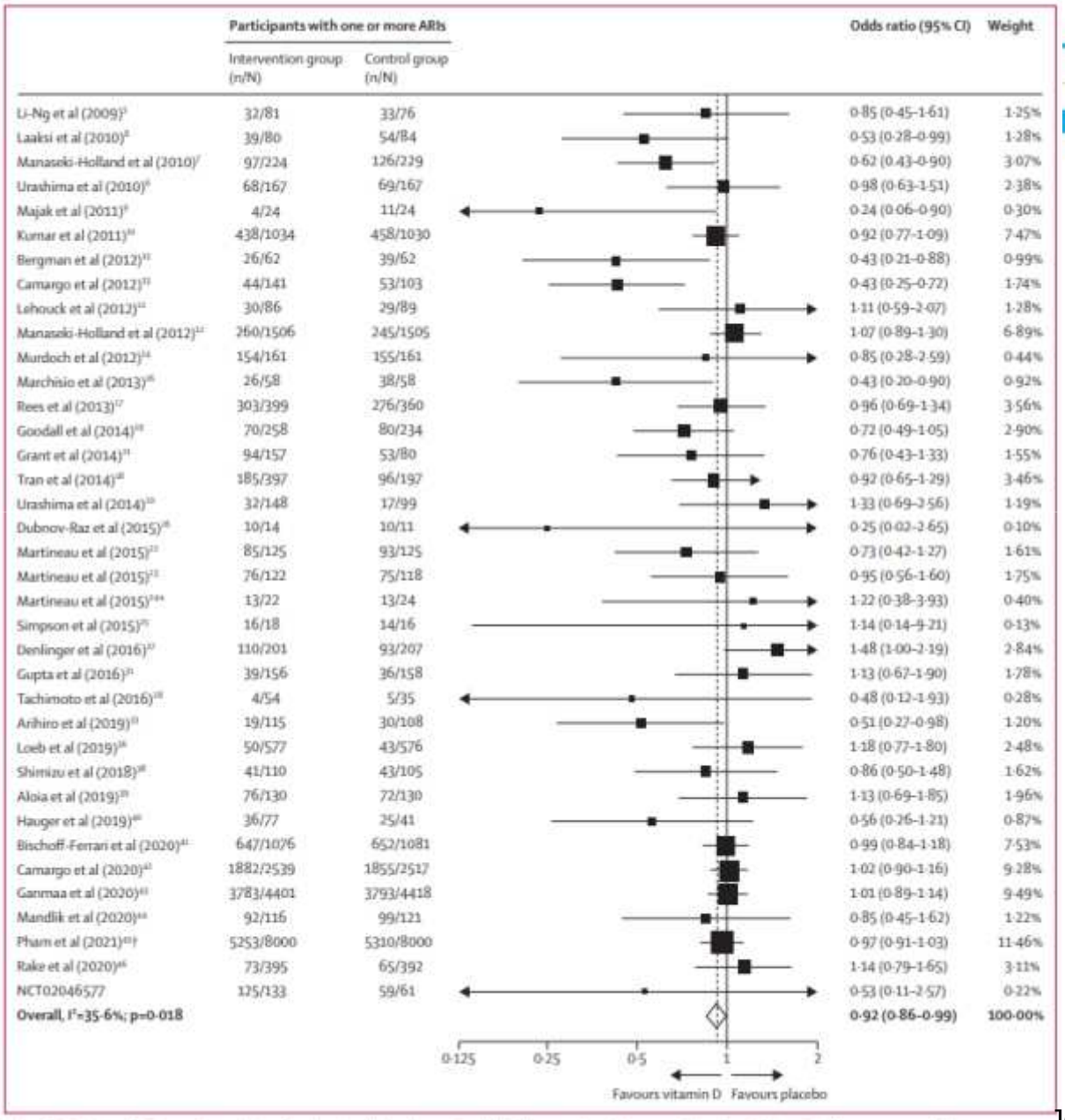



*Figure 2:* Random-effects meta-analysis of randomised, placebo-controlled trials reporting the proportion of participants with one or more ARIs

- Méta-analyse avec Random-Effect Model
  - → Préféré car hétérogénéité des OR
  - → Moins d'importance des grosses études
- 43 RCT
- 48488 patients
- Modalités d'administration de la vit D variables
- Contrôle = placebo ou vit D faible dose
- Au moins un épisode d'ARI
  - → 61,3% dans groupe Vit D
  - → 62,3% groupe contrôle
  - → OR 0,92 [0,86-0,99]

Jolliffe DA *et al*, Lancet Diabetes Endocrinol 2021

# Prévention des infections respiratoires

| | Number of trials | Proportion of participants in the intervention group with one or more events | Proportion of participants in the control group with one or more events | Odds ratio (95% CI) | $I^2$ | p value for heterogeneity |
|---|---|---|---|---|---|---|
| **Efficacy outcomes** | | | | | | |
| Upper respiratory infection* | 29 | 8578/14 569 (58·9%) | 8475/14 115 (60·0%) | 0·96 (0·91–1·02) | 1·2% | 0·45 |
| Lower respiratory infection* | 15 | 3930/13 243 (29·7%) | 3956/13 108 (30·2%) | 0·98 (0·93–1·04) | 0 | 0·63 |
| Emergency department attendance, hospital admission due to an ARI, or both | 19 | 139/10 963 (1·3%) | 149/10 850 (1·4%) | 0·90 (0·71–1·14) | 0 | 1·00 |
| Death due to ARI or respiratory failure | 34 | 14/14 688 (0·1%) | 11/14 139 (0·1%) | 1·04 (0·61–1·77) | 0 | 1·00 |
| Use of antibiotics to treat an ARI* | 14 | 2056/8638 (23·8%) | 2109/8504 (24·8%) | 0·92 (0·83–1·01) | 9·0% | 0·35 |
| Absence from work or school due to ARI | 10 | 378/1527 (24·7%) | 364/1044 (34·9%) | 0·91 (0·69–1·20) | 35·3% | 0·13 |
| **Safety outcomes** | | | | | | |
| Serious adverse event of any cause* | 36 | 567/14 937 (3·8%) | 585/14 407 (4·1%) | 0·97 (0·86–1·07) | 0 | 0·99 |
| Death due to any cause | 35 | 129/14 930 (0·9%) | 110/14 374 (0·8%) | 1·13 (0·88–1·44) | 0 | 1·00 |
| Hypercalcaemia | 22 | 51/10 370 (0·5%) | 41/10 000 (0·4%) | 1·18 (0·80–1·74) | 0 | 1·00 |
| Renal stones | 21 | 117/12 616 (0·9%) | 136/12 219 (1·1%) | 0·85 (0·67–1·11) | 0 | 1·00 |

Data are n/N (%), unless otherwise specified. ARI=acute respiratory infection. *Analysis includes a subset of participants in the trial by Pham and colleagues,[41] who completed symptom diaries.

*Table 3:* **Secondary outcomes in randomised placebo-controlled trials**

Pas de différence significative sur les autres critères de jugement

| | Number of trials | Proportion of participants in the intervention group with one or more ARIs | Proportion of participants in the control group with one or more ARIs | Odds ratio (95% CI) | $I^2$ | p value for heterogeneity |
|---|---|---|---|---|---|---|
| Overall | 37 | 14 332/23 364 (61·3%) | 14 217/22 802 (62·3%) | 0·92 (0·86–0·99) | 35·6% | 0·018 |
| Baseline 25(OH)D concentration, nmol/L* | | | | | | |
| <25·0 | 20 | 1395/1879 (74·2%) | 1433/1898 (75·5%) | 0·81 (0·57–1·15) | 44·5% | 0·017 |
| 25·0–49·9 | 29 | 3662/5022 (72·9%) | 3569/4874 (73·2%) | 1·04 (0·94–1·15) | 0·0% | 0·49 |
| 50·0–74·9 | 30 | 1929/3279 (58·8%) | 1829/3004 (60·9%) | 0·88 (0·76–1·02) | 9·3% | 0·32 |
| ≥75·0 | 26 | 1072/1742 (61·5%) | 1029/1674 (61·5%) | 1·00 (0·85–1·18) | 0·0% | 0·78 |
| Dosing frequency | | | | | | |
| Daily | 19 | 1703/3210 (53·1%) | 1672/2952 (56·6%) | 0·78 (0·65–0·94) | 53·5% | 0·003 |
| Weekly | 6 | 4482/6421 (69·8%) | 4447/6335 (70·2%) | 0·97 (0·88–1·06) | 0·0% | 0·48 |
| Once per month to once every 3 months | 12 | 8147/13 733 (59·3%) | 8098/13 515 (59·9%) | 0·98 (0·93–1·03) | 0·0% | 0·57 |
| Daily dose equivalent, IU† | | | | | | |
| <400 | 2 | 482/1175 (41·0%) | 511/1133 (45·1%) | 0·65 (0·31–1·37) | 86·3% | 0·007 |
| 400–1000 | 10 | 656/1236 (53·1%) | 627/1069 (58·7%) | 0·70 (0·55–0·89) | 31·2% | 0·16 |
| 1001–2000 | 16 | 10 593/16 961 (62·5%) | 10 674/16 898 (63·2%) | 0·97 (0·93–1·02) | 0·0% | 0·51 |
| >2000 | 7 | 2291/3462 (66·2%) | 2250/3444 (65·3%) | 1·05 (0·84–1·31) | 37·1% | 0·15 |
| Trial duration, months | | | | | | |
| ≤12 | 29 | 1977/4887 (40·5%) | 1866/4368 (42·7%) | 0·82 (0·72–0·93) | 38·1% | 0·021 |
| >12 | 8 | 12 355/18 477 (66·9%) | 12 351/18 434 (67·0%) | 0·99 (0·95–1·04) | 0·0% | 0·95 |
| Age, years* | | | | | | |
| <1·00 | 5 | 875/2901 (30·2%) | 839/2796 (30·0%) | 0·95 (0·82–1·10) | 18·7% | 0·30 |
| 1·00–15·99 | 15 | 4297/5994 (71·7%) | 4303/5877 (73·2%) | 0·71 (0·57–0·90) | 46·0% | 0·027 |
| 16·00–64·99 | 21 | 3137/4876 (64·3%) | 3087/4727 (65·3%) | 0·97 (0·93–1·09) | 11·5% | 0·31 |
| ≥65·00 | 17 | 6023/9665 (62·3%) | 6004/9475 (63·4%) | 0·96 (0·90–1·02) | 0·0% | 0·73 |
| Airway disease | | | | | | |
| Asthma only | 4 | 203/404 (50·2%) | 202/391 (51·7%) | 0·73 (0·36–1·49) | 71·7% | 0·014 |
| Chronic obstructive pulmonary disease only | 2 | 106/208 (51·0%) | 104/207 (50·2%) | 1·01 (0·68–1·51) | 0·0% | 0·71 |
| Unrestricted | 31 | 14 023/22 752 (61·6%) | 13 911/22 204 (62·7%) | 0·92 (0·86–0·99) | 33·0% | 0·040 |

Data are n/N (%), unless otherwise specified. ARI=acute respiratory infection. 25(OH)D=25-hydroxyvitamin D. IU=international units. *The number of trials in each category for this variable adds up to more than 36 because this is a participant-level variable (ie, some trials contributed data from participants who were included in more than one category). †Data from two trials (Tran and colleagues[18] and NCT02046577) that included higher-dose, lower-dose, and placebo groups were excluded from this subgroup analysis because the higher-dose and lower-dose groups spanned the 1000 IU/day cutoff, making them unclassifiable.

***Table 2:*** **Number of participants in randomised placebo-controlled trials with at least one ARI, overall and stratified by potential effect-modifiers**

- Pas de différence d'effet selon le taux basal de 25(OH)vitamine D

Jolliffe DA *et al*, Lancet Diabetes Endocrinol 2021

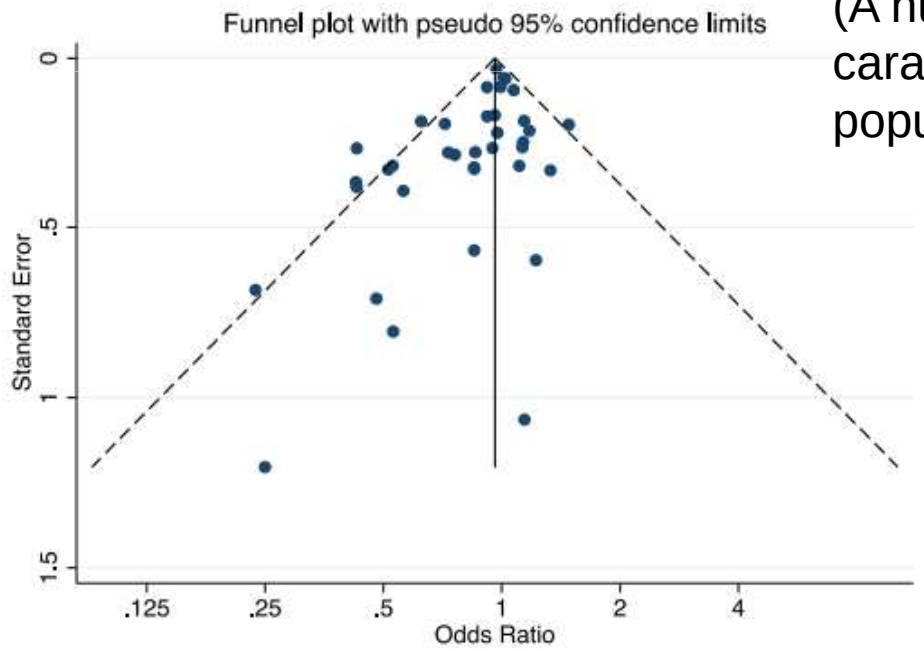
# Comment supplémenter pour prévenir les infections respiratoires ?

- Impact significatif de la vitamine D si administrée dans les conditions suivantes :
  - → 400 à 1000 unités /j
  - → Administration quotidienne
  - → Chez des sujets de 1 à 16 ans

# Prévention des infections respiratoires - Limites

- Hétérogénéité des études – un effet plus marqué dans un sous-groupe de patients est possible
- Possible biais de publication en faveur des études positives

**Figure S10:** Funnel plot of placebo-controlled RCTs reporting proportion of participants experiencing 1 or more acute respiratory infection.




(A nuancer en fonction des caractéristiques de chaque population)

Egger's test for publication bias: P=0.007

Jolliffe DA *et al*, Lancet Diabetes Endocrinol 2021

# VITAMINE D ET COVID-19

# Rationnel

- Facteurs de risque de COVID-19 grave = FDR de carence en vitamine D
  → Âge, ethnie, obésité

- COVID grave = maladie auto-inflammatoire
  → Intérêt potentiel de l'activité anti-inflammatoire de la vitamine D

- Multiples études montrant un lien entre déficit en vitamine D et mortalité par COVID

# Etudes observationnelles

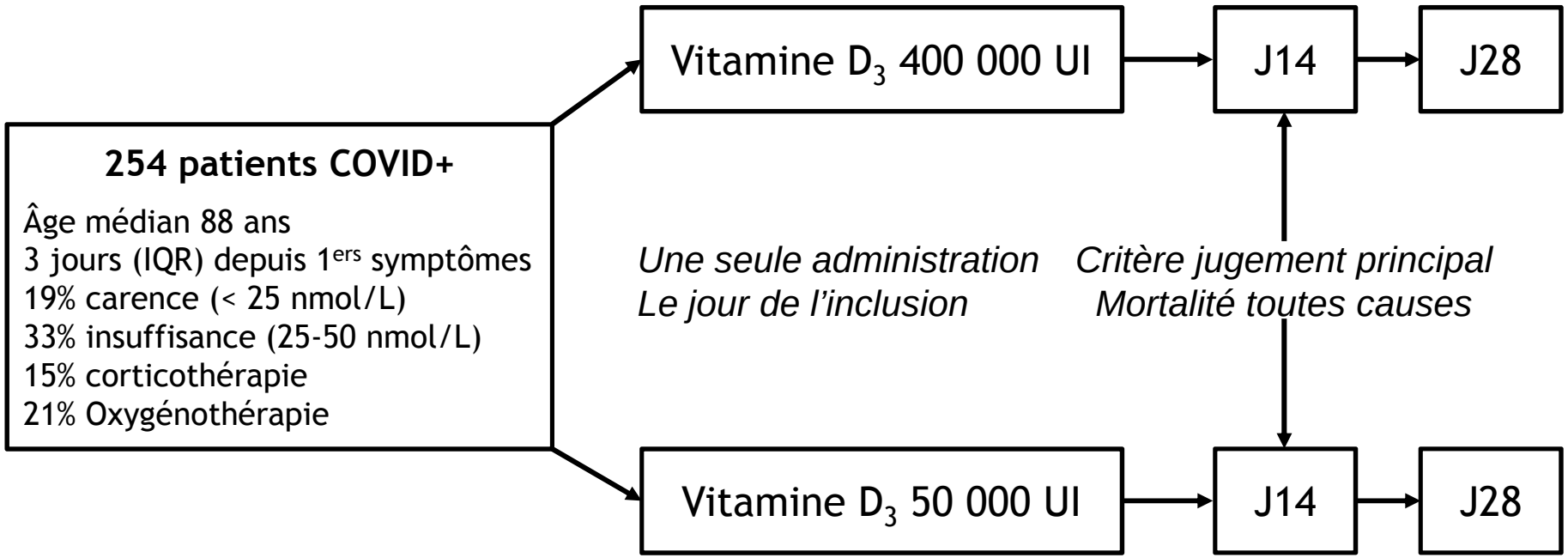
**Table 1.** Characteristics and comparisons of participants with COVID-19 according to the study groups ($n$ = 77).

| | | Study Groups | | | | *p*-Value * | | |
|---|---|---|---|---|---|---|---|---|
| | All COVID-19 Participants ($n$ = 77) | Group 1 Regular Vitamin D Supplementation ($n$ = 29) | Group 2 Vitamin D Supplementation After COVID-19 Diagnosis ($n$ = 16) | Group 3 Non-Supplemented Comparator Group ($n$ = 32) | Overall ($n$ = 77) | Group 1 Versus Group 3 ($n$ = 61) | Group 2 Versus Group 3 ($n$ = 48) | Group 1 Versus Group 2 ($n$ = 45) |
| **Demographical data** | | | | | | | | |
| Age (years), med (IQR) | 88 (85–92) | 88 (87–93) | 85 (84–89) | 88 (84–92) | 0.22 | 0.98 | 0.12 | 0.10 |
| Female gender | 38 (49.4) | 20 (69.0) | 5(31.3) | 13 (40.6) | **0.02** | **0.027** | 0.52 | **0.015** |
| GIR score (/6), med (IQR) | 4 (2–4) | 4 (3–4) | 4 (3–5) | 4 (2–5) | 0.36 | 0.63 | 0.34 | 0.13 |
| **Comorbidities** | | | | | | | | |
| Severe undernutrition † | 21 (27.3) | 9 (31.0) | 3 (18.8) | 9 (28.1) | 0.67 | 0.80 | 0.73 | 0.49 |
| Hematological and solid cancers | 27 (35.1) | 10 (34.5) | 4 (25.0) | 13 (40.6) | 0.56 | 0.62 | 0.29 | 0.74 |
| Hypertension | 49 (63.6) | 18 (62.1) | 10 (62.5) | 21 (65.6) | 0.95 | 0.77 | 0.83 | 0.98 |
| Cardiomyopathy | 42 (54.5) | 13 (44.8) | 11 (68.8) | 18 (56.3) | 0.30 | 0.37 | 0.40 | 0.12 |
| Glycated hemoglobin (%), med (IQR) | 6.2 (5.8–6.7) | 6.0 (5.5–6.6) | 6.4 (6.0–8.2) | 6.2 (5.9–6.7) | 0.16 | 0.19 | 0.34 | 0.08 |
| **Hospitalization** | | | | | | | | |
| Number of acute health issues at hospital admission, med (IQR) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 3.5 (2.0–5.0) | 2.5 (1.0–4.0) | 0.22 | 0.18 | 0.14 | 0.62 |
| CRP at admission (mg/L), med (IQR) | 59.5 (19.5–135.0) | 44.0 (19.0–110.0) | 69.0 (15.5–140.0) | 59.0 (29.0–166.0) | 0.47 | 0.21 | 0.67 | 0.63 |
| Use of antibiotics ‡ | 59 (76.6) | 23 (79.3) | 14 (87.5) | 22 (68.8) | 0.32 | 0.349 | 0.29 | 0.69 |
| Use of systemic corticosteroids | 13 (16.9) | 6 (20.7) | 2 (12.5) | 5 (15.6) | 0.79 | 0.607 | 1.00 | 0.69 |
| Use of pharmacological treatments of respiratory disorders ‖ | 10 (13.0) | 1 (3.5) | 2 (12.5) | 7 (21.9) | 0.10 | 0.055 | 0.70 | 0.29 |
| **COVID-19 outcomes** | | | | | | | | |
| Severe COVID-19 § | 17 (22.1) | 3 (10.3) | 4 (25.0) | 10 (31.3) | 0.14 | **0.047** | 0.75 | 0.23 |
| 14-day mortality | 15 (19.5) | 2 (6.9) | 3 (18.8) | 10 (31.3) | 0.06 | **0.017** | 0.50 | 0.33 |

Etude GERIA-COVID : 77 patients consécutifs hospitalisés en gériatrie à Angers pour COVID mars – mai 2020
Analyse selon la stratégie de supplémentation en vitamine D

# L'essai COVIT-TRIAL

Randomisation 1:1
Ouvert



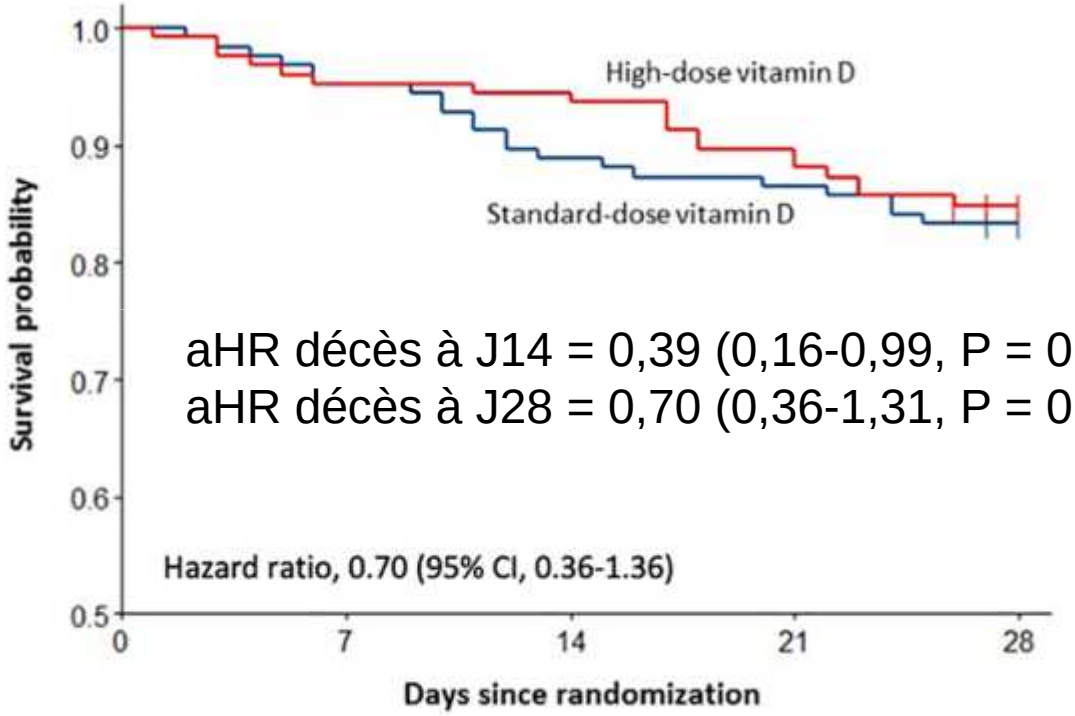

*Exclusion*

$O_2$ ≥ 5 L/min
Supplémentation en Vit D ≥ 800 UI/j
Patients moribonds



Annweiler C *et al*, Plos Medicine 2022

# Mortalité




aHR décès à J14 = 0,39 (0,16-0,99, P = 0,049)
aHR décès à J28 = 0,70 (0,36-1,31, P = 0,29)

| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Standard-dose vitamin D | 126 | 120 | 112 | 109 | 101 |
| High-dose vitamin D | 126 | 120 | 119 | 113 | 104 |

# Commentaires et limites

- Essai en ouvert
- Conçu et mené par un expert du sujet
- Hypercalcémie chez 3 patients dans le groupe HD
- Schéma d'administration non optimal ?
  → Nécessité d'une dose d'entretien ?

- Un autre essai négatif mais design moins robuste
  → Murai IH et al, JAMA 2021

# SEPSIS ET CHOC SEPTIQUE ET PATIENTS EN SOINS INTENSIFS

# Association entre carence en vitamine D et infections en réanimation

- Méta-analyse 14 études observationnelles, 9715 patients
- Carence en 25-OH vitamine $D_3$ (< 50 nmol/L) à l'entrée associée à
  - → Augmentation du risque d'infection acquise en réa RR 1,49
  - → Augmentation du risque de sepsis RR 1,46
  - → Augmentation de la mortalité à J30 RR 1,42
  - → Augmentation de la mortalité hospitalière RR 1,79

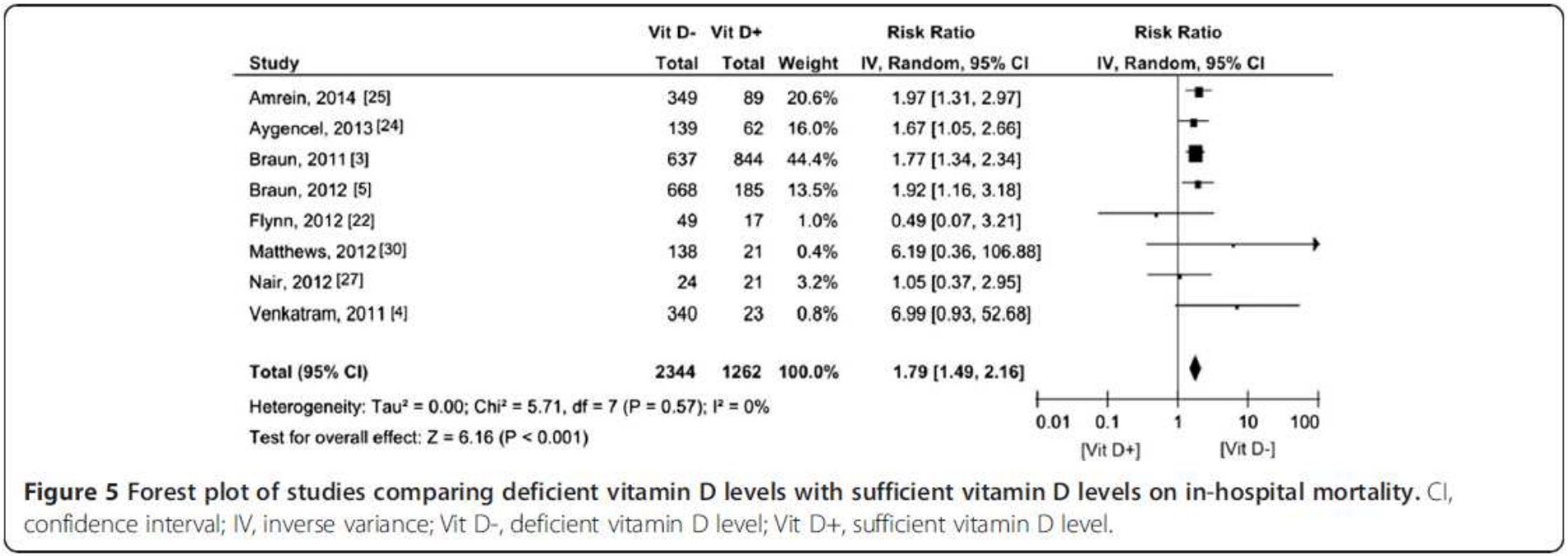
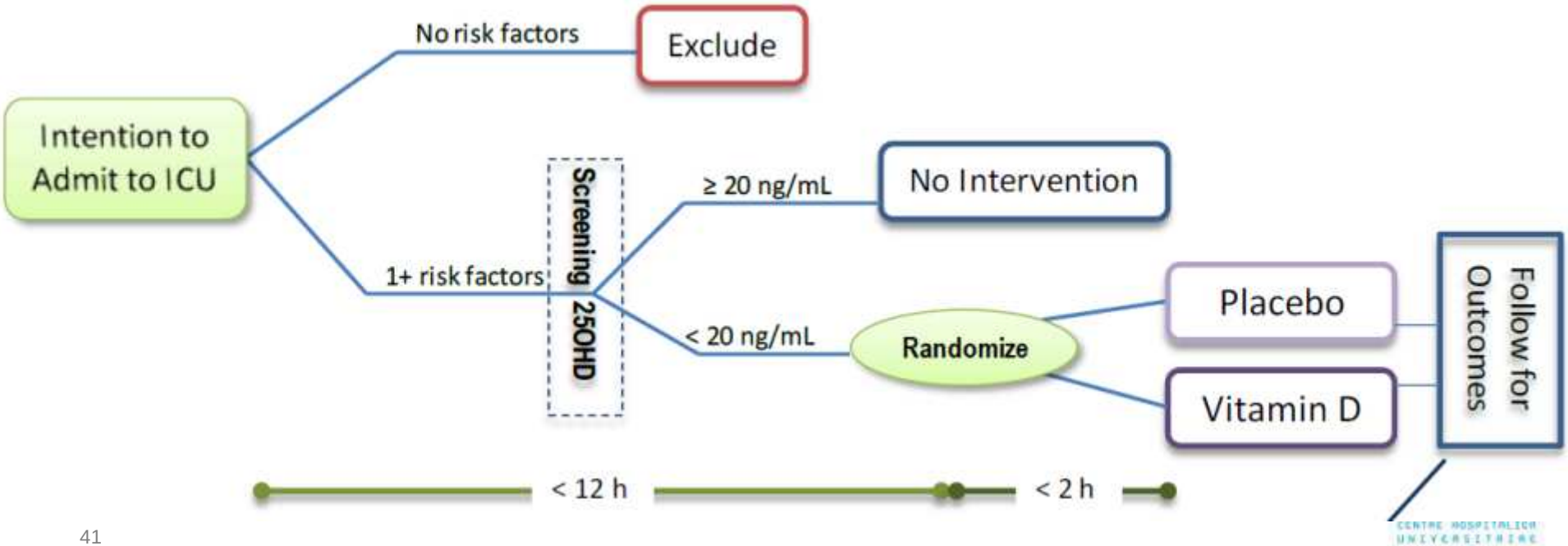



**Figure 5 Forest plot of studies comparing deficient vitamin D levels with sufficient vitamin D levels on in-hospital mortality.** CI, confidence interval; IV, inverse variance; Vit D-, deficient vitamin D level; Vit D+, sufficient vitamin D level.

# L'essai VIOLET

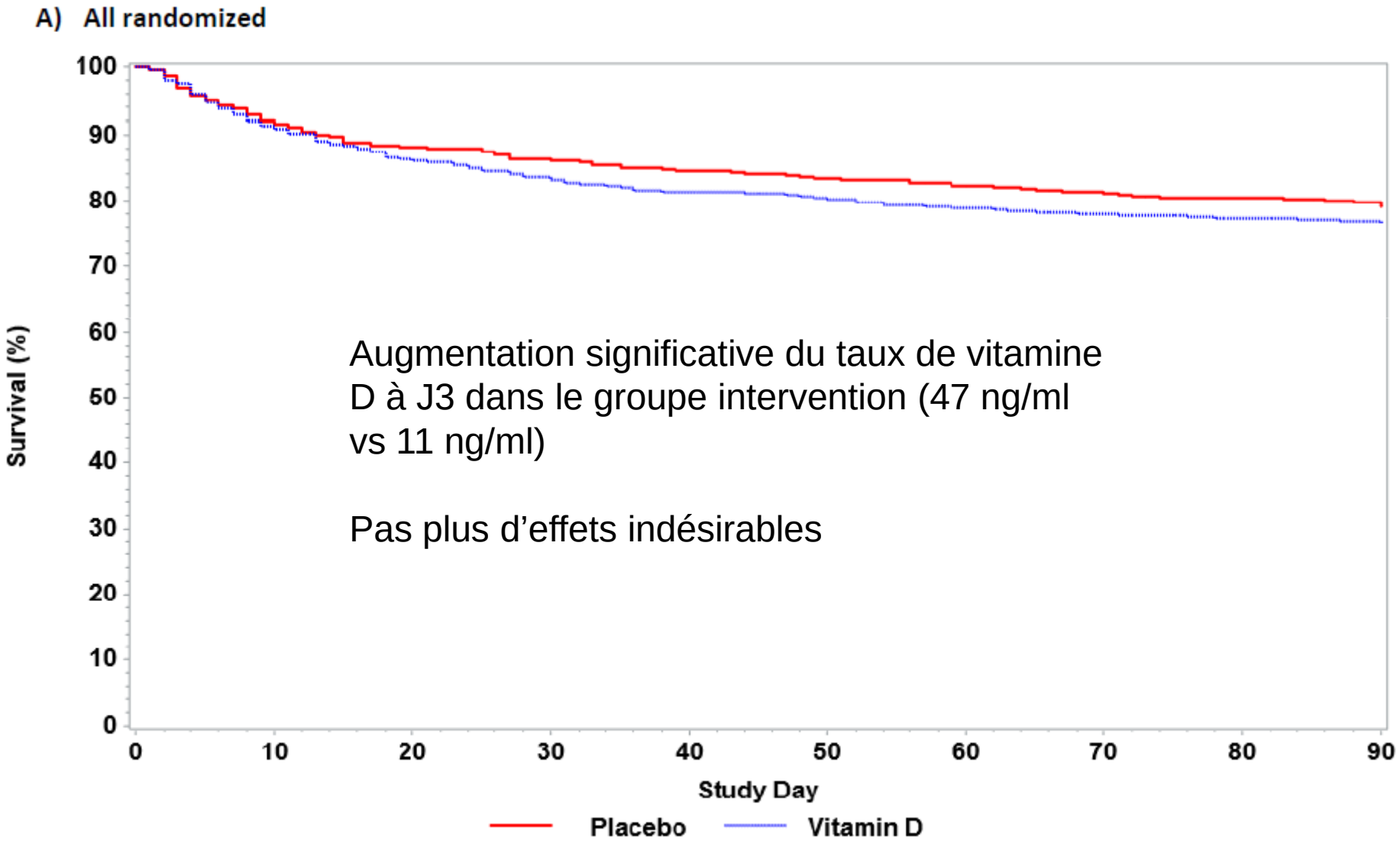
- Essai randomisé contrôlé en double aveugle vs placebo
- 1360 patients de réanimation à haut risque de décès ayant un probable déficit en vitamine D (test au lit du patient)
- Randomisation 1:1 540 000 UI de vitamine $D_3$ ou placebo (PO/SNG)
- CJP : mortalité à J90






Violet Trial / PETAL clinical trials Network, NEJM 2019

# Impact sur mortalité toutes causes à J90

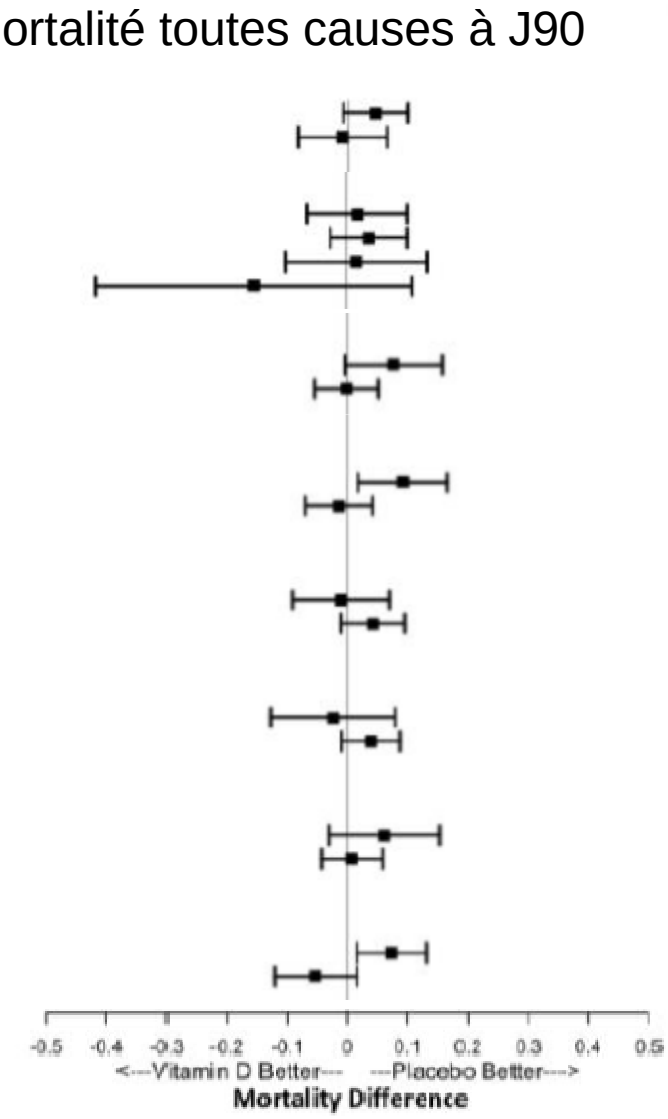



Augmentation significative du taux de vitamine D à J3 dans le groupe intervention (47 ng/ml vs 11 ng/ml)

Pas plus d'effets indésirables

# Analyse en sous-groupes

Mortalité toutes causes à J90




| Subgroup (N) | Placebo | Vitamin D | Difference | 95% CI |
|---|---|---|---|---|
| Age, years | | | | |
| Age < 60 (N=725) | 0.131 | 0.175 | 0.044 | (-0.008,0.097) |
| Age ≥ 60 (N=612) | 0.307 | 0.298 | -0.009 | (-0.082,0.064) |
| Baseline 25OHD Level (2), ng/mL | | | | |
| < 10 (N=448) | 0.252 | 0.270 | 0.018 | (-0.064,0.099) |
| 10-19.9 (N=611) | 0.173 | 0.210 | 0.037 | (-0.026,0.099) |
| 20-29.9 (N=186) | 0.195 | 0.212 | 0.016 | (-0.100,0.133) |
| ≥ 30 (N=40) | 0.318 | 0.167 | -0.152 | (-0.411,0.108) |
| Risk Factor — Sepsis | | | | |
| Yes (N=445) | 0.214 | 0.291 | 0.077 | (-0.003,0.158) |
| No (N=892) | 0.206 | 0.204 | -0.002 | (-0.055,0.051) |
| Risk Factor — Pneumonia | | | | |
| Yes (N=482) | 0.178 | 0.270 | 0.092 | (0.018,0.165) |
| No (N=855) | 0.225 | 0.212 | -0.013 | (-0.069,0.042) |
| Risk Factor — Shock | | | | |
| Yes (N=457) | 0.257 | 0.247 | -0.010 | (-0.090,0.070) |
| No (N=880) | 0.184 | 0.226 | 0.042 | (-0.011,0.095) |
| Risk Factor — Mechanical Ventilation | | | | |
| Yes (N=294) | 0.295 | 0.270 | -0.024 | (-0.127,0.079) |
| No (N=1043) | 0.184 | 0.223 | 0.039 | (-0.010,0.088) |
| Risk Factor — Multiple | | | | |
| Yes (N=364) | 0.253 | 0.314 | 0.061 | (-0.031,0.154) |
| No (N=973) | 0.193 | 0.201 | 0.008 | (-0.042,0.058) |
| Risk Factor — Infectious vs. Non-Infectious | | | | |
| Infectious (N=812) | 0.196 | 0.270 | 0.074 | (0.016,0.132) |
| Non-infectious (N=525) | 0.228 | 0.176 | -0.053 | (-0.121,0.016) |

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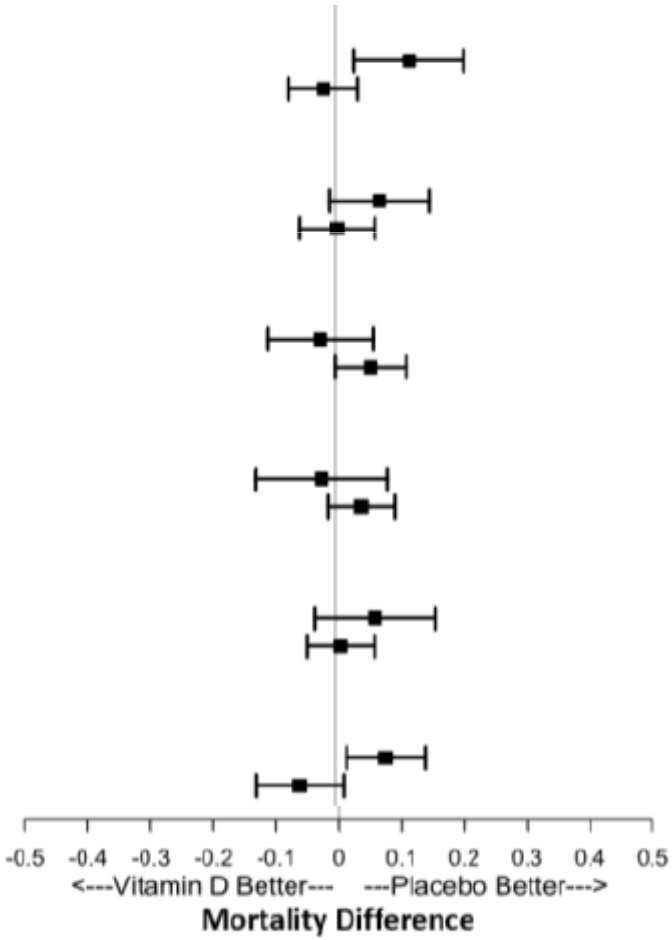
# Analyse en sous-groupe

Mortalité à J90 - Patients avec une carence en vitamine D confirmée

| Subgroup (N) | Placebo | Vitamin D | Difference | 95% CI |
|---|---|---|---|---|
| Risk Factor — Sepsis | | | | |
| Yes (N=350) | 0.213 | 0.337 | 0.124 | (0.032,0.216) |
| No (N=709) | 0.203 | 0.183 | -0.020 | (-0.079,0.038) |
| Risk Factor — Pneumonia | | | | |
| Yes (N=380) | 0.184 | 0.259 | 0.074 | (-0.009,0.157) |
| No (N=679) | 0.218 | 0.221 | 0.003 | (-0.059,0.066) |
| Risk Factor — Shock | | | | |
| Yes (N=383) | 0.271 | 0.246 | -0.025 | (-0.112,0.063) |
| No (N=676) | 0.170 | 0.229 | 0.060 | (-0.000,0.120) |
| Risk Factor — Mechanical Ventilation | | | | |
| Yes (N=237) | 0.269 | 0.246 | -0.023 | (-0.134,0.088) |
| No (N=822) | 0.188 | 0.232 | 0.044 | (-0.011,0.100) |
| Risk Factor — Multiple | | | | |
| Yes (N=299) | 0.252 | 0.319 | 0.067 | (-0.035,0.169) |
| No (N=760) | 0.190 | 0.199 | 0.009 | (-0.047,0.066) |
| Risk Factor — Infectious vs. Non-Infectious | | | | |
| Infectious (N=633) | 0.199 | 0.284 | 0.085 | (0.019,0.151) |
| Non-infectious (N=426) | 0.216 | 0.157 | -0.059 | (-0.133,0.014) |



# Vitamine D et états septiques graves

- Pas d'intérêt d'une supplémentation en bolus chez les patients atteints d'infections graves
  - → Possible surmortalité chez les patients en sepsis

- Domaines d'incertitude :
  - → Autres modalités d'administration ?

# VITAMINE D ET CONSOMMATION D'ANTIBIOTIQUES

# Essai D-Health

- 21315 sujets âgés de 60 ans ou plus, Australie
- Randomisation : vit D3 60 000 UI ou placebo une fois par mois pendant 5 ans
- CJP : mortalité toutes causes pendant l'essai
- Analyse a posteriori des données sur l'antibiothérapie
  - → Lien avec données de santé (assurance maladie)

Pham H et al, Journal of Infectious Diseases 2022
Neale RE et al, Lancet Diabetes and Endocrinology 2022

# Population de l'étude

| aracteristic | Placebo, No. (%) (n = 9735) | Vitamin D, No. (%) (n = 9762) |
|---|---|---|
| x | | |
| Men | 5327 (54.7) | 5336 (54.7) |
| Women | 4408 (45.3) | 4426 (45.3) |
| e, y | | |
| 60–64 | 2399 (24.6) | 2387 (24.5) |
| 65–69 | 2677 (27.5) | 2690 (27.6) |
| 70–74 | 2657 (27.3) | 2657 (27.2) |
| ≥75 | 2002 (20.6) | 2028 (20.8) |
| dy mass index, kg/m² | | |
| <25 | 2869 (29.6) | 2985 (30.7) |
| ≥25 | 6820 (70.4) | 6738 (69.3) |
| Missing | 46 | 39 |
| oking history | | |
| Never | 5253 (54.4) | 5315 (54.9) |
| Ex-smoker | 3959 (41.0) | 3998 (41.3) |
| Current | 438 (4.5) | 377 (3.9) |
| Missing | 85 | 72 |
| lf-rated overall health | | |
| Excellent or very good | 5323 (55.5) | 5396 (56.2) |
| Good, fair, or poor | 4271 (44.5) | 4205 (43.8) |
| Missing | 141 | 161 |
| lf-rated quality of life | | |
| Excellent or very good | 6459 (67.8) | 6444 (67.5) |
| Good, fair, or poor | 3070 (32.2) | 3100 (32.5) |
| Missing | 206 | 218 |
| dicted serum 25(OH)D concentration, nmol/L | | |
| <50 | 2393 (24.6) | 2325 (23.8) |
| ≥50 | 7342 (75.4) | 7437 (76.2) |

Pas de dosage du taux de vitamine D
Faible proportion attendue de sujets carencés

Pham H et al, Journal of Infectious Diseases 2022

# Consommation d'ATB dans l'essai D-Health

**Table 2. Effects of Vitamin D Supplementation on Antibiotic Prescriptions Dispensed**

| Outcomes | Placebo (n = 9735, PYAR = 47 306) | | | Vitamin D (n = 9762, PYAR = 47 491) | | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of People With ≥1 Episode | No. of Episodes | Incidence Rate per 1 PYAR[a] (95% CI) | No. of People With ≥1 Episodes | No. of Episodes | Incidence Rate per 1 PYAR[a] (95% CI) | IRR[a] (95% CI) | Rate Difference[a] per 1 PYAR (95% CI) |
| Antibiotic prescription episodes[b] | 8292 | 45 367 | 0.96 (.94–.98) | 8288 | 44 754 | 0.94 (.92–.96) | .98 (.95–1.01) | −0.02 (−.05 to .01) |
| Total antibiotic prescriptions | 8292 | 71 098 | 1.51 (1.47–1.55) | 8288 | 69 467 | 1.46 (1.42–1.49) | .97 (.93–1.00) | −0.05 (−.10 to .00) |
| Repeat episodes, exploratory analysis[c] | 5762 | 16 083 | 0.34 (.33–.35) | 5707 | 15 614 | 0.32 (.32–.33) | .96 (.93–1.00) | −0.01 (−.03 to .00) |
| Repeat episodes, sensitivity analysis[d] | 5218 | 12 900 | 0.27 (.26–.28) | 5148 | 12 435 | 0.26 (.25–.27) | .96 (.92–1.00) | −0.01 (−.02 to .00) |
| | Placebo, No. Episodes/No. Surveys (%) (n = 9684) | | | Vitamin D, No. Episodes/No. Surveys (%) (n = 9724) | | | OR[e] (95% CI) | |
| Antibiotics for UTI[f] | 2775/47 028 (5.9) | | | 2826/47 238 (6.0) | | | 1.01 (.94–1.09) | |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; PYAR, person year at risk; UTI, urinary tract infection.

[a]Incidence rates, rate differences, and incidence rate ratios from negative binomial regression models that included the randomization stratification variables of sex, age, and state of residence at baseline.

[b]Prescriptions dispensed within 21 days of another prescription comprised a single episode.

[c]A repeat antibiotic prescription episode was defined as a prescription episode with more than 1 record.

[d]Repeat episodes based on antibiotics prescribed on the same day were excluded.

[e]Outcomes pooled across 5 surveys; OR estimated using logistic regression models (using generalized estimating equations with an exchangeable correlation matrix) with adjustment for sex, age, and state of residence at baseline.

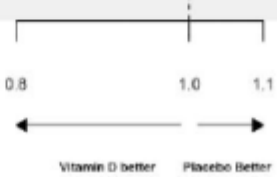
[f]People with missing data for all 5 annual surveys were excluded (n = 89).



Pham H et al, Journal of Infectious Diseases 2022

# Consommation d'ATB dans l'essai D-Health

| Subgroup | Placebo Incidence rate (95% CI) | Vitamin D Incidence rate (95% CI) | IR Ratio (95% CI) | *P* value for Interaction |
|---|---|---|---|---|
| **All participants** | 0.96 (.94–.98) | 0.94 (.92–.96) | 0.98 (.95–1.01) | |
| **Age** | | | | .055 |
| 60 to < 70 y | 0.85 (.82–.87) | 0.81 (.78–.83) | 0.95 (.91–.99) | |
| ≥ 70 y | 1.08 (1.05–1.11) | 1.09 (1.06–1.12) | 1.01 (.97–1.05) | |
| **Sex** | | | | .84 |
| Men | 0.83 (.81–.86) | 0.81 (.79–.84) | 0.98 (.94–1.02) | |
| Women | 1.09 (1.06–1.13) | 1.07 (1.04–1.11) | 0.98 (.94–1.03) | |
| **Body mass index** | | | | .28 |
| < 25 kg/m² | 0.86 (.83–.90) | 0.82 (.79–.86) | 0.96 (.90–1.01) | |
| ≥ 25 kg/m² | 1.00 (.97–1.02) | 0.99 (.97–1.02) | 0.99 (.96–1.03) | |
| **Predicted 25(OH)D concentration** | | | | .052 |
| < 50 nmol/L | 1.07 (1.02–1.12) | 1.00 (.95–1.04) | 0.93 (.87–.99) | |
| ≥ 50 nmol/L | 0.90 (.90–.95) | 0.92 (.90–.95) | 1.00 (.96–1.03) | |
| **Overall health** | | | | .04 |
| Excellent, very good | 0.78 (.75–.80) | 0.79 (.77–.81) | 1.02 (.98–1.06) | |
| Good, fair, poor | 1.19 (1.15–1.23) | 1.14 (1.10–1.18) | 0.95 (.91–1.00) | |




Pham H et al, Journal of Infectious Diseases 2022

# D-Health – Résultats globaux

- Pas d'impact sur mortalité
- Pas d'impact sur infections respiratoires
- Taux de cancer plus élevé dans le groupe vitamine D
  - → HR 1,15 (0,96-1,39)
  - → HR 1,24 (1,01-1,54) si exclusion des deux premières années de suivi

# Complexité de la question

- Intervention
  - → Forme de vitamine D ($D_2$/$D_3$)
  - → Dose de vitamine D
  - → Rythme d'administration (bolus/quotidienne)
- Population
  - → Carence en vitamine D O/N
  - → Etat nutritionnel global
  - → Enfants/adultes
- Condition
  - → Infections bactériennes
  - → Mycobactéries
  - → Infections virales
  - → Infections respiratoires

**Pas de réponse globale**

# Conclusions

- Enormément de moyens consacrés à la question
- Pas de réponse définitive
- Possible effet bénéfique dans des conditions précises

- **Il ne paraît pas justifié de prescrire une supplémentation pour la prévention ou le traitement des infections**

- Mais il est toujours pertinent de s'assurer d'apports alimentaires corrects…