

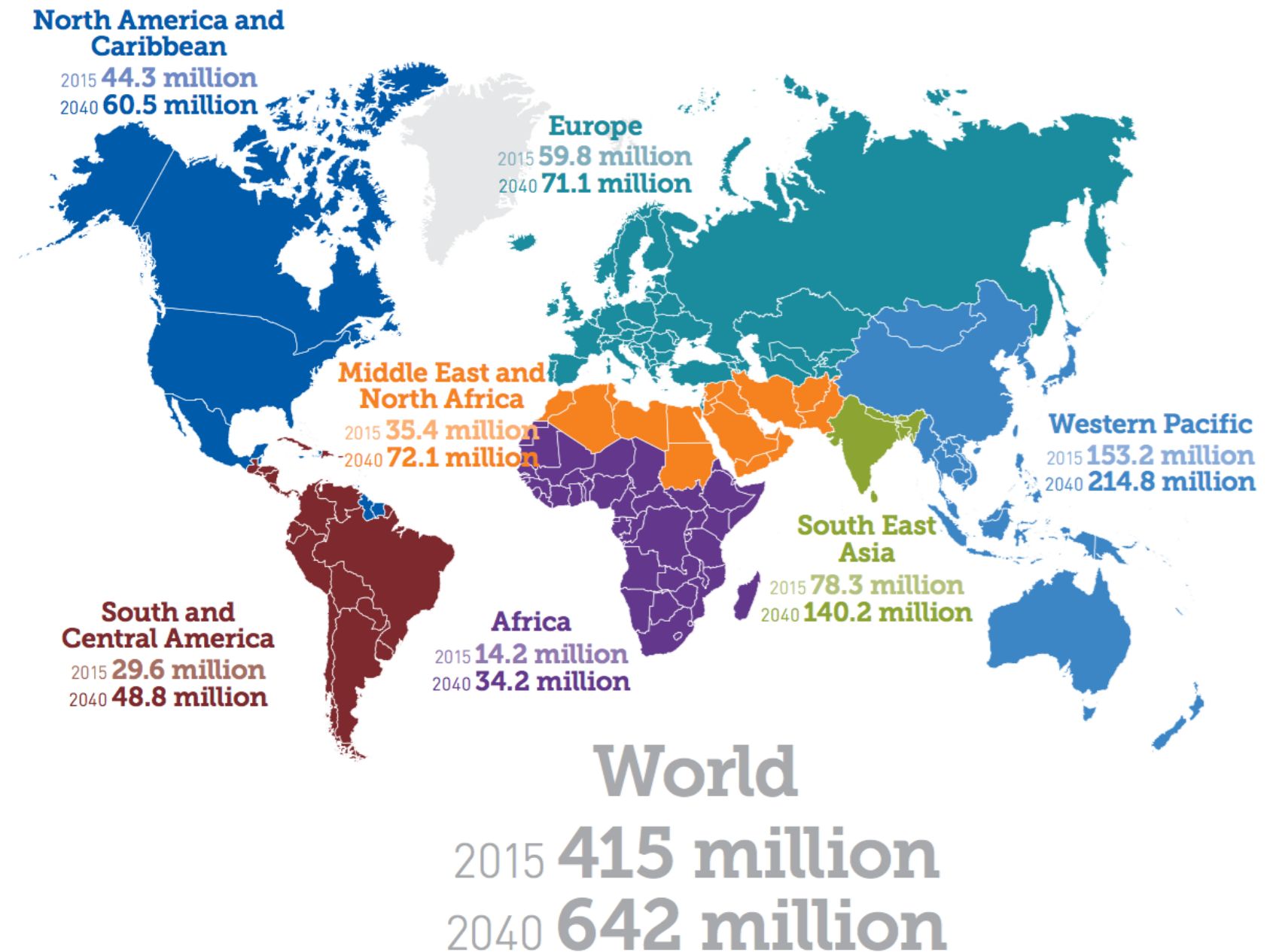
# **TUBERCULOSIS FÁRMACO RESISTENTE CO-MORBILIDADES**

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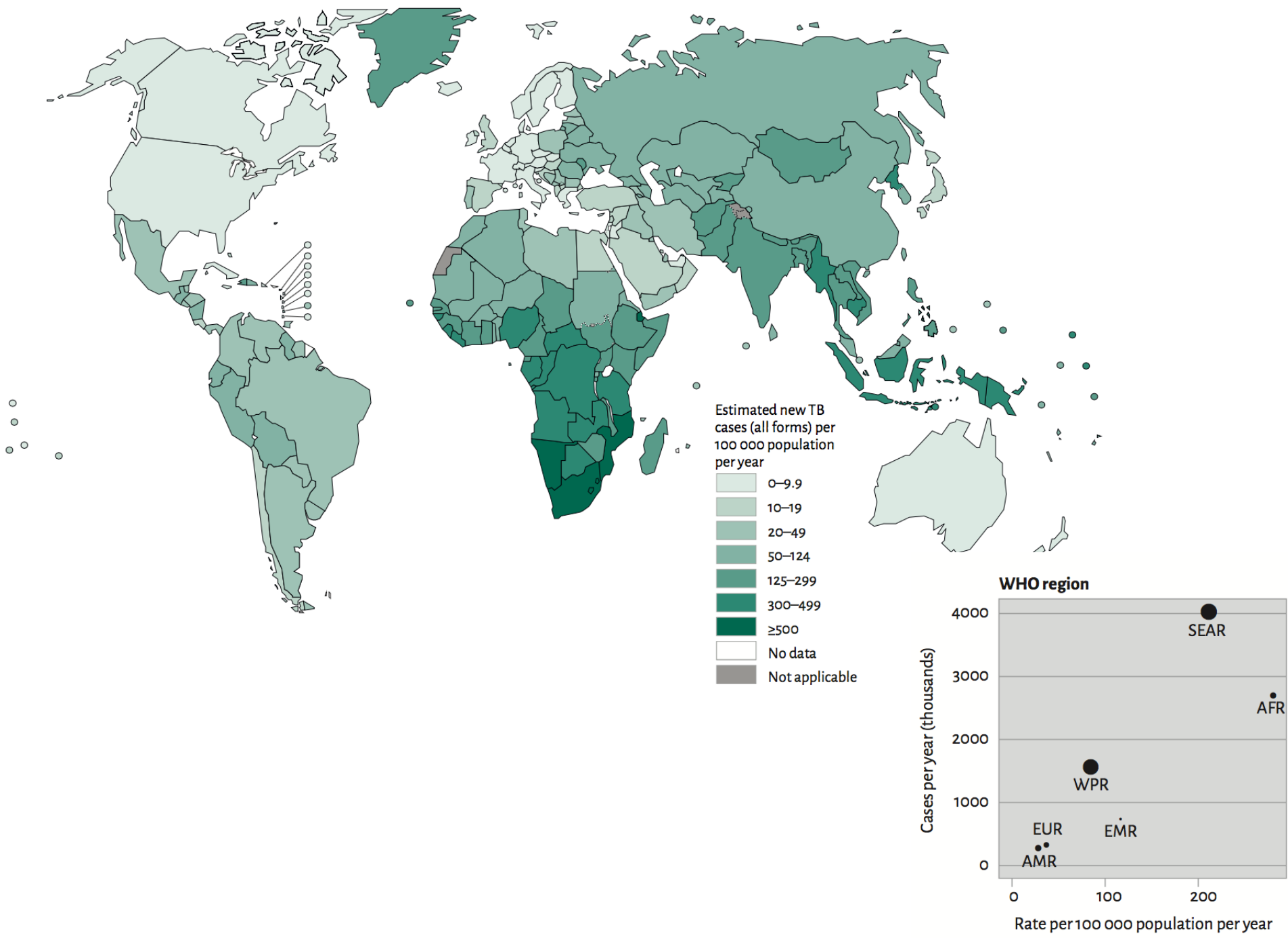
**DRA. MARCELA MUÑOZ**



## Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



Estimated TB incidence rates, 2014



# CARGA MUNDIAL

## DIABETES MELLITUS (2014)

- 365 millones viven con
- DM
- 6 millones de casos
- cada año
- 4.6 millones de muertes por DM

## TUBERCULOSIS (2014)

- 9.6 millones de casos nuevos
- 1.5 millones de muertes

# Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

- 13 estudios observacionales
- 1,786,212 participantes
- 17,698 casos de TBP

# RIESGO DE TBP EN DM2

| Study           | Sample Size      | RR   | 95% CI       |
|-----------------|------------------|------|--------------|
| <b>Cohort</b>   | <b>Cases/Pop</b> |      |              |
| Kim, 1995 [7]   | 5105/814713      | 3.57 | (3.07, 5.16) |
| John, 2001 [32] | 166/1251         | 2.24 | (1.38, 3.65) |
| Chen, 2006 [30] | 29/756           | 3.07 | (1.14, 8.26) |

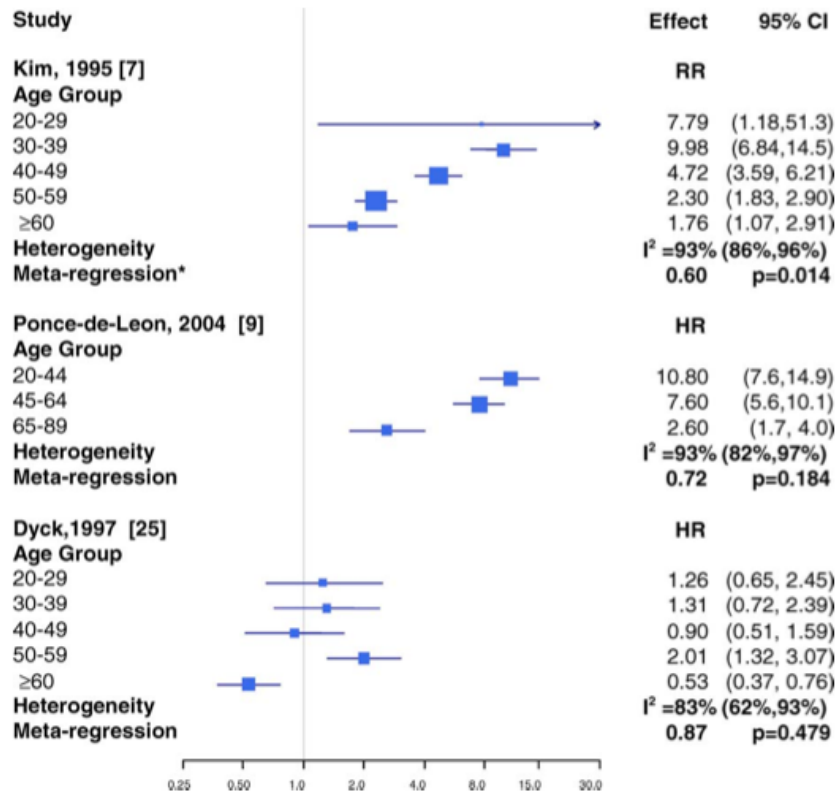
**A pesar de la heterogeneidad de los estudios, es muy evidente la asociación entre DM2 y el riesgo de tuberculosis.**

|                         |            |                           |                  |
|-------------------------|------------|---------------------------|------------------|
| Pablos-Mendez, 1997 [8] | 6236/37388 | 1.81                      | (1.58, 1.78)     |
| Brassard, 2006 [31]     | 386/38600  | 1.50                      | (1.15, 1.90)     |
| Coker, 2006 [37]        | 334/334    | 7.83                      | (2.37, 25.9)     |
| Jick, 2006 [33]         | 497/1966   | 3.80                      | (2.30, 6.10)     |
| Perez, 2006 [11]        | 3847/66714 | 1.65                      | (1.50, 1.81)     |
| <b>Heterogeneity:</b>   |            | <b>I<sup>2</sup> =68%</b> | <b>(34%,85%)</b> |

|                         |                  |                           |                   |
|-------------------------|------------------|---------------------------|-------------------|
| <b>Other*</b>           | <b>Cases/Pop</b> |                           |                   |
| Ponce-de-Leon, 2004 [9] | 581/21230        | 6.00                      | (5.00, 7.20)      |
| Dyck, 2007 [25]         | 1118/791673      | 0.99                      | (0.80, 1.23)      |
| <b>Heterogeneity:</b>   |                  | <b>I<sup>2</sup> =99%</b> | <b>(99%,100%)</b> |

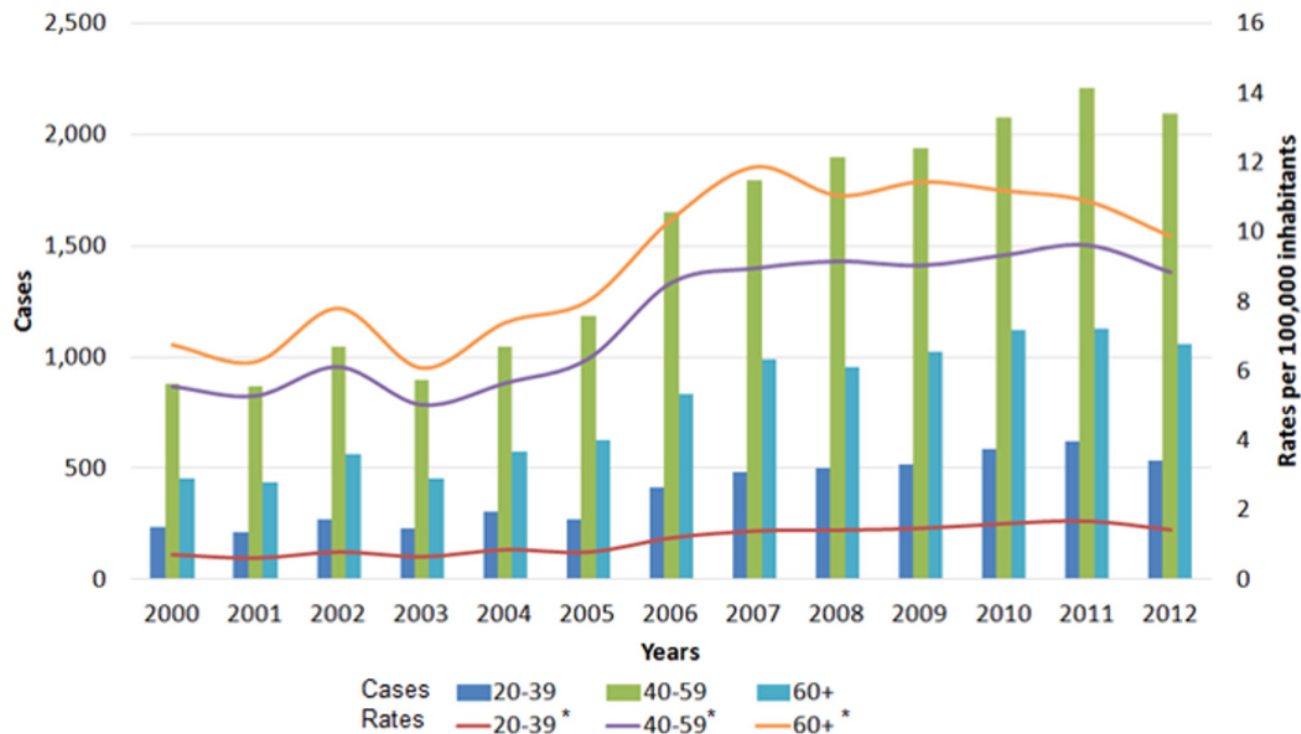


# EFECTO CLARO DE LA EDAD



Se observa mayor  
riesgo en  
pacientes jóvenes  
(<40 años).

# Association of Pulmonary Tuberculosis and Diabetes in Mexico: Analysis of the National Tuberculosis Registry 2000–2012



Incremento de la asociación TBP + DM2:

2000 → 2.82/1000,00 HAB el

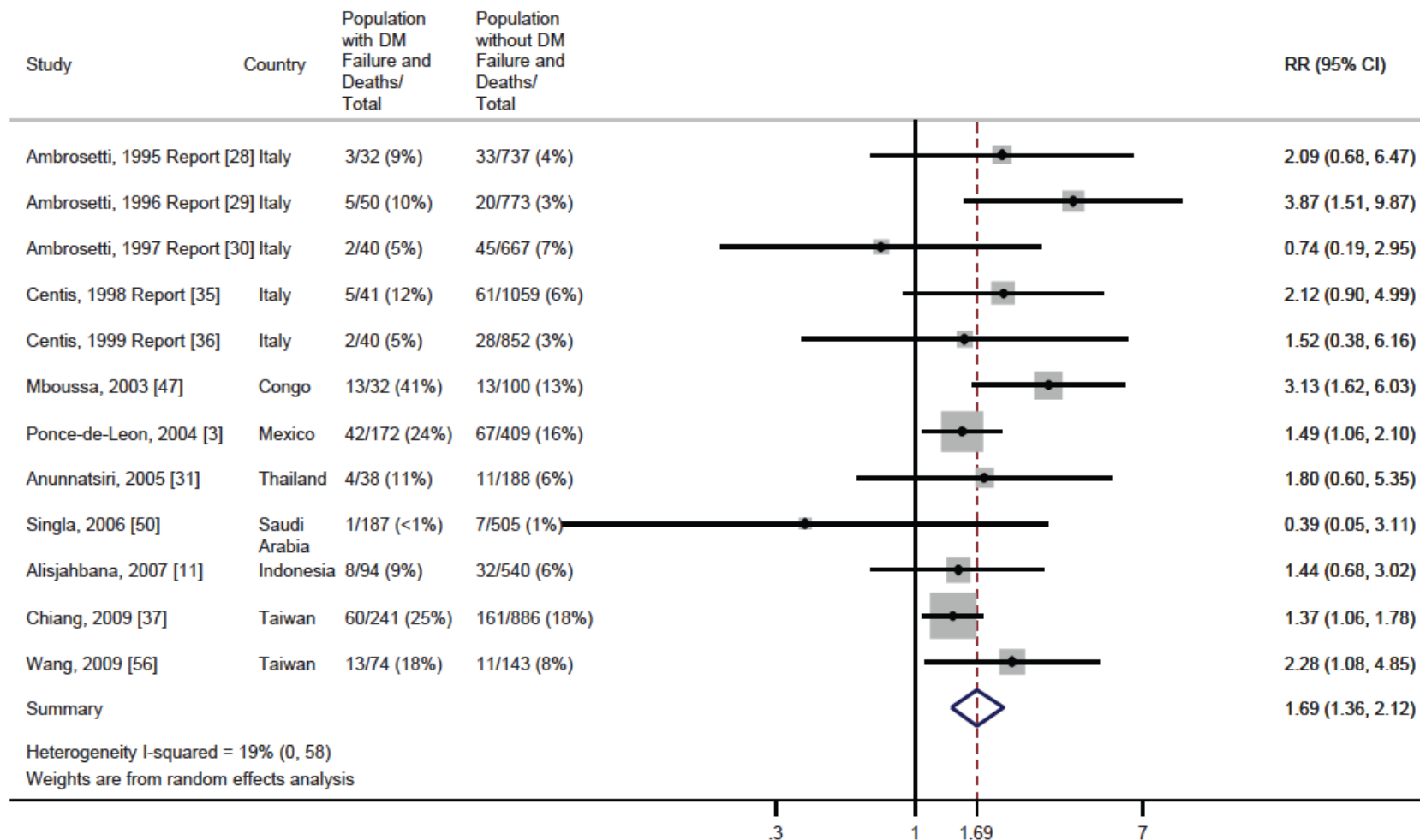
2012 → 5.16% el 2012

INCREMENTO DE LA INCIDENCIA ANUAL DEL 82.64%

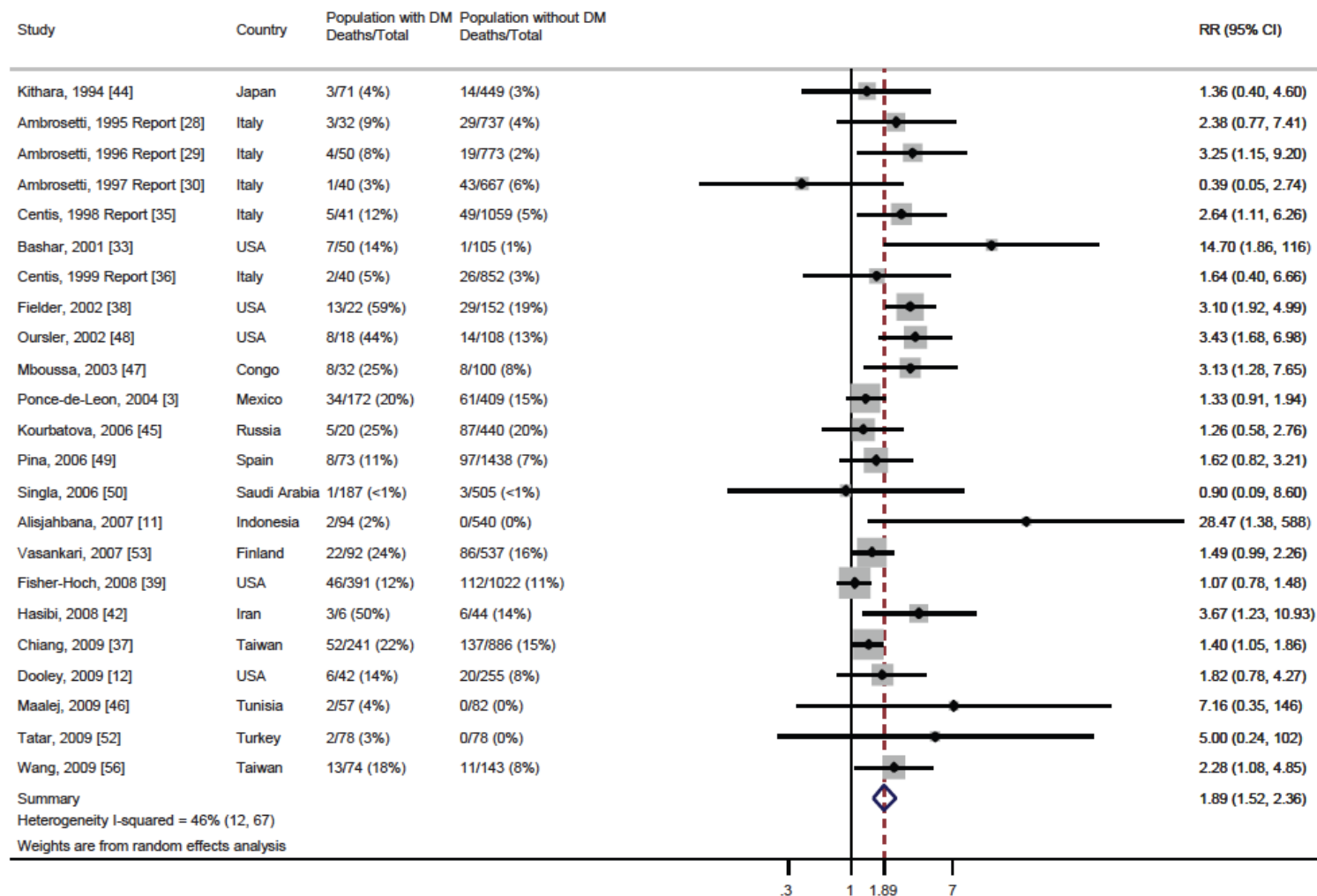
# The impact of diabetes on tuberculosis treatment outcomes: A systematic review

- 33 estudios
- 9 reportaron conversión bacteriológica
- 12 reportaron muerte y falla al Tx.

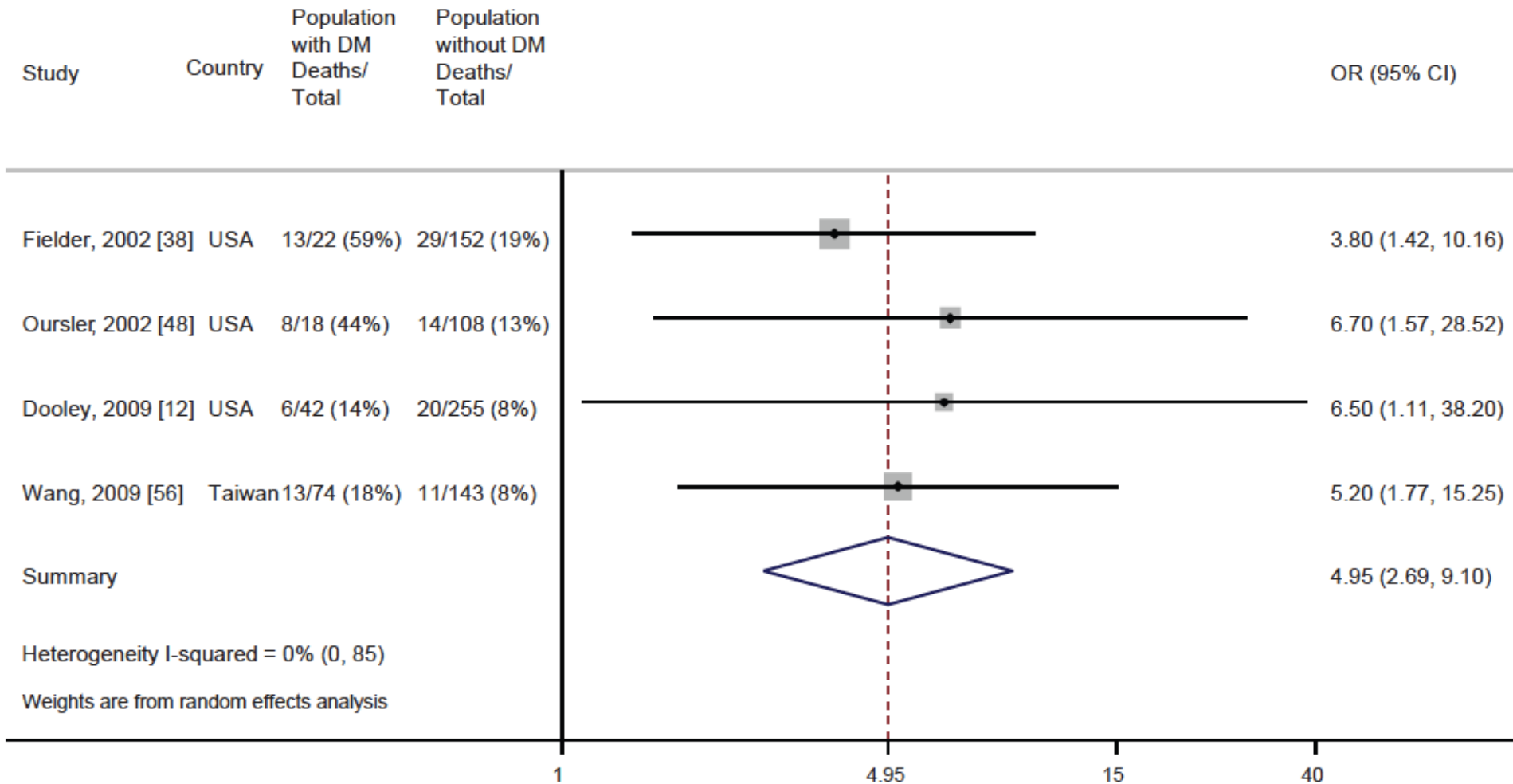
# FALLO A TX Y MUERTE



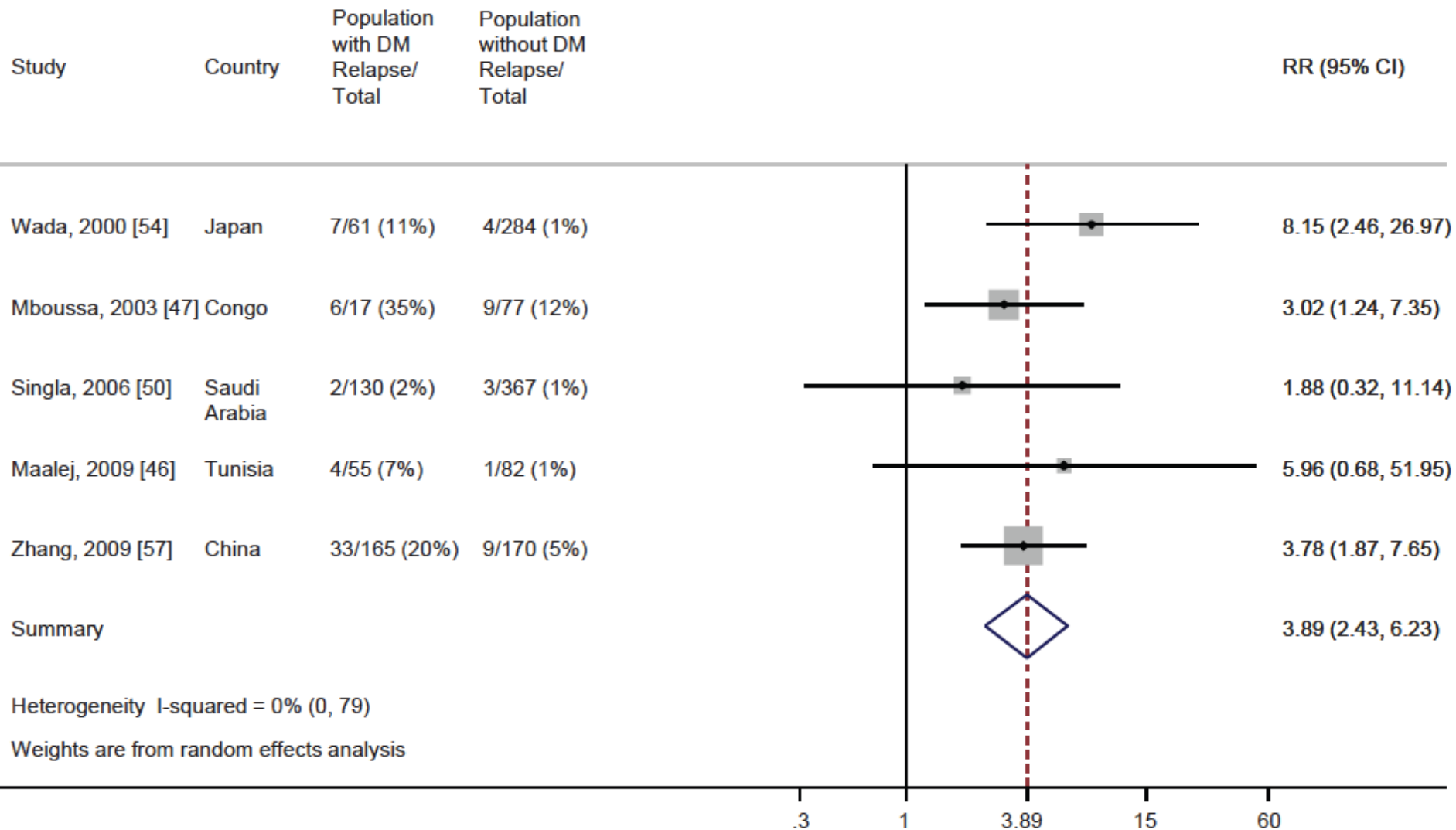
# RIESGO NO AJUSTADO DE MUERTE



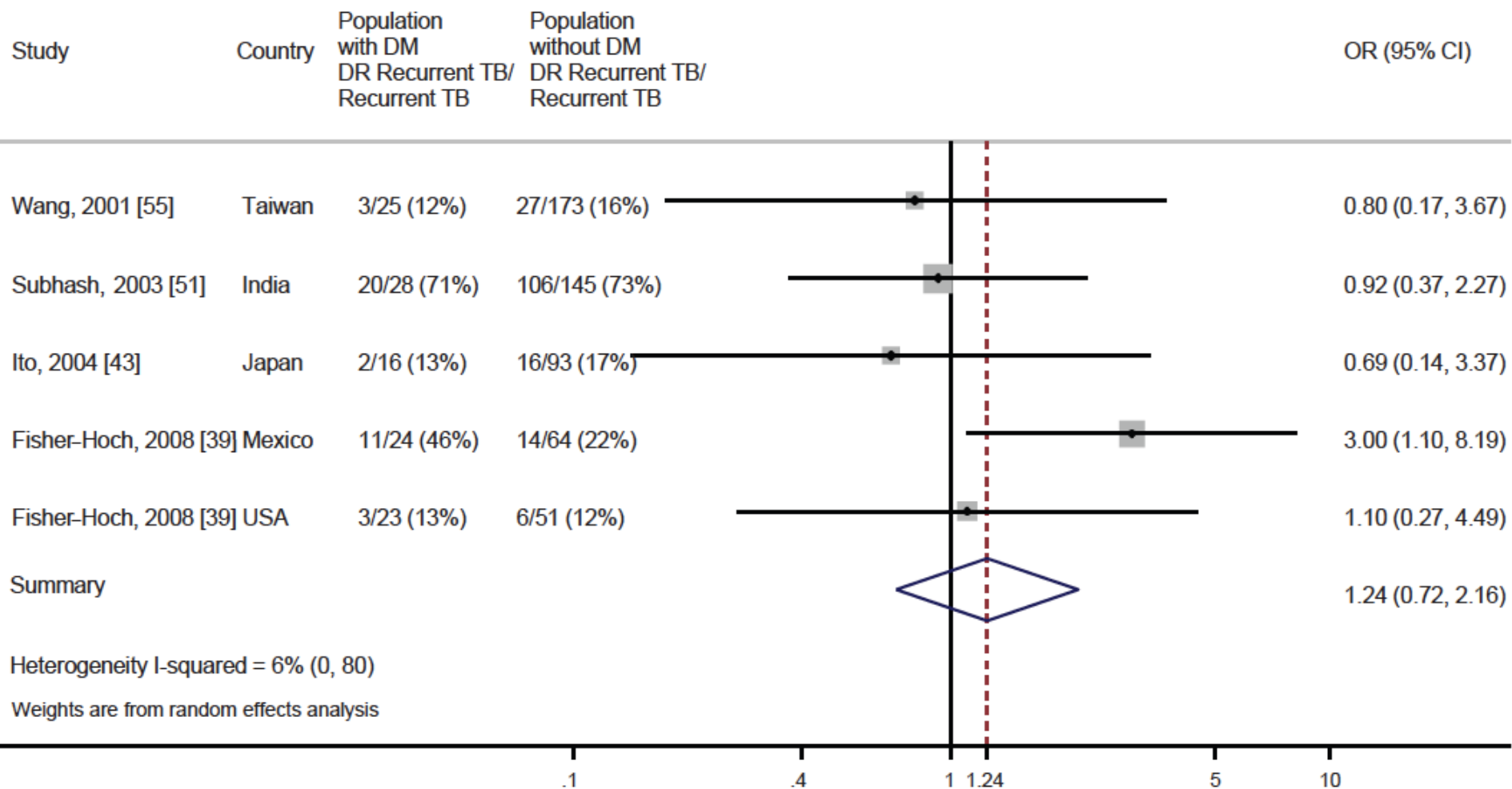
# RIESGO DE MUERTE AJUSTADO A LA EDAD



# RIESGO DE RECAÍDA



# RIESGO DE FÁRMACO-RESISTENCIA



# Association of Pulmonary Tuberculosis and Diabetes in Mexico: Analysis of the National Tuberculosis Registry 2000–2012

**Table 3. Adjusted odds ratio (OR)\* and 95% Confidence Intervals (CI) for treatment failure, Mexico 2000–2012.**

| Independent variable | No. of patients | Adjusted OR for treatment failure (95%CI) | <i>p</i> -value |
|----------------------|-----------------|-------------------------------------------|-----------------|
| All patients         |                 |                                           |                 |
| DM                   | 118,701         | 1.34 (1.11 to 1.61)                       | 0.002           |
| Women                |                 |                                           |                 |
| DM                   | 45,754          | 1.62 (1.31 to 2.01)                       | <0.001          |
| Men                  |                 |                                           |                 |
| DM                   | 72,947          | 1.21 (1.01 to 1.44)                       | 0.038           |

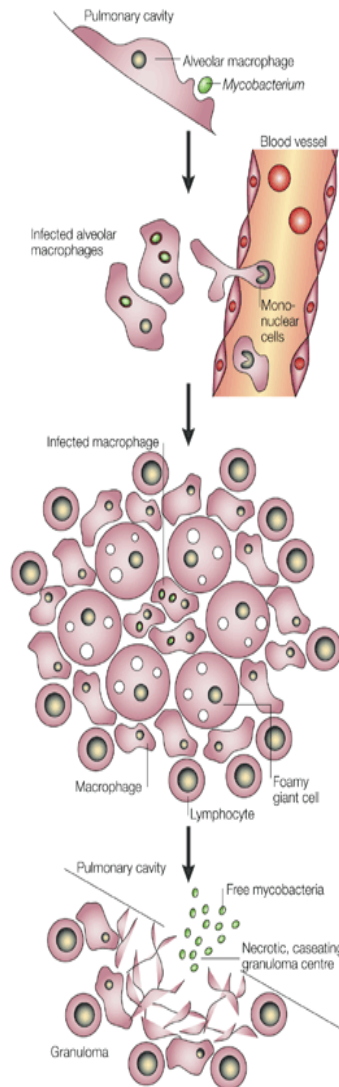
**Table 2. Adjusted odds ratio (OR)\* and 95% Confidence Intervals (CI) for MDR TB, Mexico 2000–2012.**

| Independent variable | No. of patients | Adjusted OR for MDR TB (95% CI) | <i>p</i> -value |
|----------------------|-----------------|---------------------------------|-----------------|
| All patients         |                 |                                 |                 |
| DM                   | 1,874           | 1.28 (1.14 to 1.44)             | <0.001          |
| Women                |                 |                                 |                 |
| DM                   | 553             | 1.06 (0.83 to 1.38)             | 0.604           |
| Men                  |                 |                                 |                 |
| DM                   | 1,321           | 1.44 (1.17 to 1.76)             | 0.001           |

# COMO LA DIABETES INCREMENTA EL RIESGO DE TB?

- Alteraciones Inmunológicas
- Estado de inflamación crónica inespecífica

# ALTERACIONES INMUNOLOGICAS



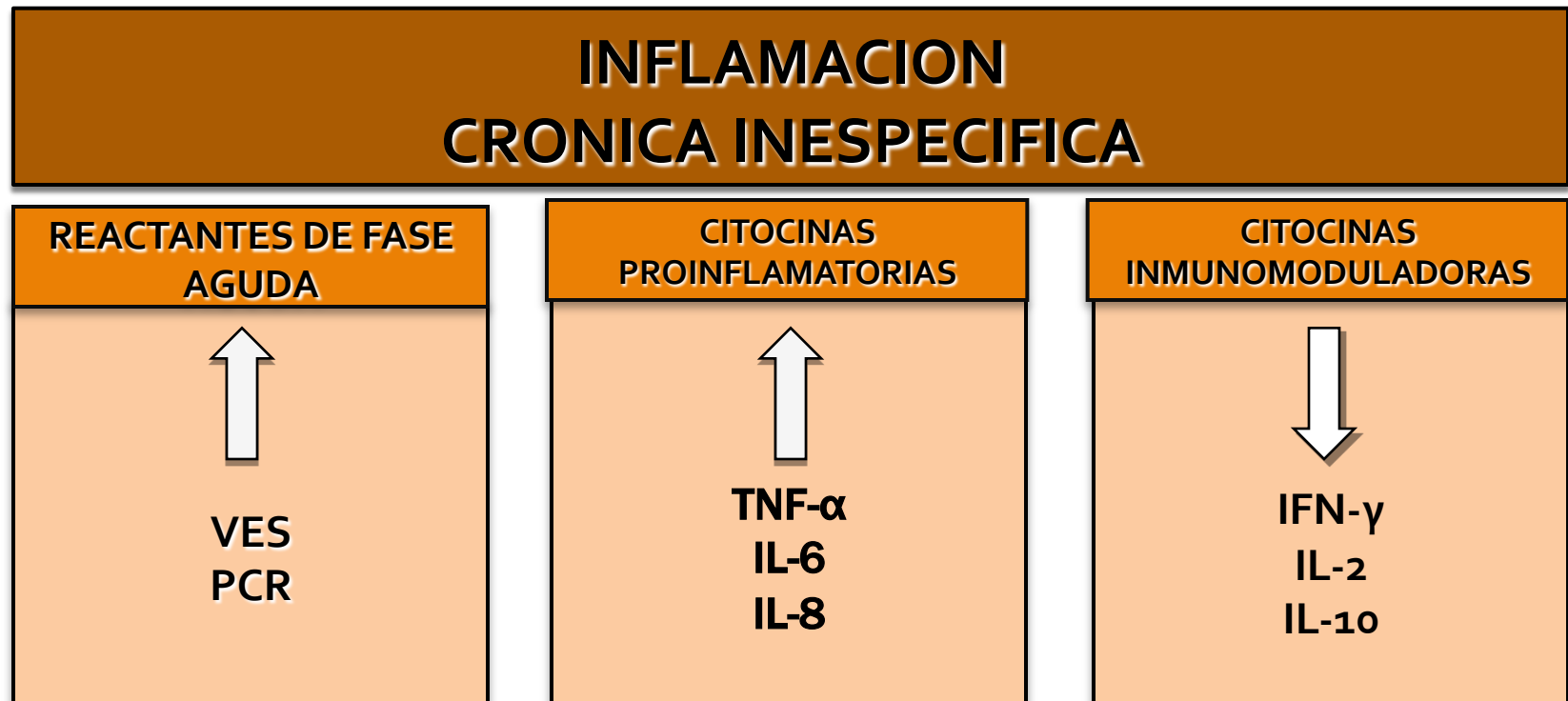
## ALTERACIONES EN LA RESPUESTA INMUNE INATA

- ↓ Fagocitosis Mtb.
- ↓ Expresión de genes relacionados:
  - Presentación de Atg mico bacterianos
  - Expresión de péptidos antimicrobianos: catelicidina

## ALTERACIONES EN LA RESPUESTA INMUNE ADAPTATIVA

- Respuesta Th1 variable (IFN-g, IL-2)
- ↑ Respuesta Th17
- ↑ Respuesta celular desordenada e inefectiva

# INFLAMACIÓN Y DIABETES MELLITUS



# Does enhanced diabetes management reduce the risk and improve the outcome of tuberculosis?

## ■ Registro medico nacional en Taiwan

- DM-p4p: Programa de control estricto para DM2 → 79,491
- DM-no-p4p: Pacientes en seguimiento habitual → 100,000
- Pacientes sin DM2 → 100,000

## ■ Desenlaces:

- Primario: Casos nuevos de tuberculosis
- Secundario: Desenlace al tratamiento

**Table 3** 1-year, 2-year and 3-year cumulative incidence rates of TB per 100 000 population in a random sample of DM-p4p, DM-non-p4p and non-DM patients, from the 2008–2009 NHI database\*

|             | DM-p4p         |                    |                      | DM-non-p4p     |                    |                      | Non-DM         |                    |                      |
|-------------|----------------|--------------------|----------------------|----------------|--------------------|----------------------|----------------|--------------------|----------------------|
|             | Number at risk | Active TB /100 000 |                      | Number at risk | Active TB /100 000 |                      | Number at risk | Active TB /100 000 |                      |
|             |                | Cumulative number  | Cumulative incidence |                | Cumulative number  | Cumulative incidence |                | Cumulative number  | Cumulative incidence |
| Total       | 79 471         |                    |                      | 100 000        |                    |                      | 100 000        |                    |                      |
| 2008 cohort | 46 226         |                    |                      | 85 810         |                    |                      | 48 334         |                    |                      |
| 1-year      |                | 63                 | 136                  |                | 239                | 279                  |                | 33                 | 68                   |
| 2-year      |                | 130                | 281                  |                | 429                | 500                  |                | 61                 | 126                  |
| 3-year      |                | 204                | 441                  |                | 603                | 703                  |                | 95                 | 197                  |
| 2009 cohort | 33 245         |                    |                      | 14 190         |                    |                      | 51 666         |                    |                      |
| 1-year      |                | 34                 | 102                  |                | 63                 | 444                  |                | 49                 | 95                   |
| 2-year      |                | 85                 | 256                  |                | 81                 | 571                  |                | 85                 | 165                  |

\* DM-p4p = patients with DM enrolled in a pay-for-performance (p4p) programme for DM; DM-non-p4p = patients with DM not enrolled in the p4p programme for DM; non-DM = non-diabetic patients.

DM = diabetes mellitus; TB = tuberculosis; NHI = National Health Insurance.

**Incidencia acumulada total: 1153 casos (0.4%)**

- **DM-no-p4p: 684 (0.7%)**
- **DM-p4p: 289 (0.4%)**
- **No DM: 180 (0.2%)**

**Table 4** Factors associated with incident TB in 2008–2010 in a sample of 279 471 patients from the 2008–2009 NHI database

|                                       | Total<br><i>n</i> | TB<br><i>n</i> (%) | Univariate<br>OR (95%CI) | Multivariate<br>aOR (95%CI) |
|---------------------------------------|-------------------|--------------------|--------------------------|-----------------------------|
| Total                                 | 279 471           | 1 153 (0.4)        |                          |                             |
| DM status*                            |                   |                    |                          |                             |
| Non-DM                                | 100 000           | 180 (0.2)          | Reference                |                             |
| DM-p4p                                | 79 471            | 289 (0.4)          | 2.03 (1.68–2.44)         | 1.12 (0.93–1.36)            |
| DM-non-p4p                            | 100 000           | 684 (0.7)          | 3.82 (3.24–4.50)         | 1.84 (1.55–2.17)            |
| Sex                                   |                   |                    |                          |                             |
| Male                                  | 134 725           | 818 (0.6)          | 2.63 (2.32–2.99)         | 2.73 (2.41–3.09)            |
| Female                                | 144 746           | 335 (0.2)          | Reference                | Reference                   |
| Age, years                            |                   |                    |                          |                             |
| <40                                   | 61 336            | 59 (0.1)           | Reference                | Reference                   |
| 40–49                                 | 36 670            | 105 (0.3)          | 2.98 (2.17–4.10)         | 2.30 (1.67–3.17)            |
| 50–59                                 | 63 562            | 199 (0.3)          | 3.26 (2.44–4.36)         | 2.48 (1.83–3.35)            |
| 60–69                                 | 56 827            | 233 (0.4)          | 4.28 (3.21–5.69)         | 3.39 (2.49–4.55)            |
| 70–79                                 | 44 080            | 326 (0.7)          | 7.74 (5.86–10.21)        | 6.11 (4.55–8.20)            |
| ≥80                                   | 16 996            | 231 (1.4)          | 14.31 (10.75–19.06)      | 10.56 (7.81–14.29)          |
| Complication/comorbidity <sup>†</sup> |                   |                    |                          |                             |
| No                                    | 175 318           | 556 (0.3)          | Reference                |                             |
| Any                                   | 104 153           | 597 (0.6)          | 1.81 (1.61–2.03)         | 1.01 (0.90–1.14)            |

\* DM-p4p = patients with DM enrolled in a pay-for-performance (p4p) programme for DM; DM-non-p4p = patients with DM not enrolled in the p4p programme for DM; non-DM = non-diabetic patients.

<sup>†</sup> Included retinopathy, nephropathy, neuropathy, peripheral vascular disease, cardiovascular disease and cerebrovascular disease.

TB = tuberculosis; NHI = National Health Insurance; OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio; DM = diabetes mellitus.

## Desenlace: al tratamiento:

**Table 5** Factors associated with the outcome of TB among 766 incident TB cases that occurred in 2008–2009 in a sample of 279 471 patients from the 2008–2009 NHI database

|                | Total<br><i>n</i> | Success<br><i>n</i> (%) | Died<br><i>n</i> (%) | Other<br><i>n</i> (%) |
|----------------|-------------------|-------------------------|----------------------|-----------------------|
| Number (row %) | 766               | 544 (71.0)              | 141 (18.4)           | 81 (10.6)             |
| DM status*     |                   |                         |                      |                       |
| DM-p4p         | 164               | 124 (75.6)              | 21 (12.8)            | 19 (11.6)             |
| DM-non-p4p     | 492               | 339 (68.9)              | 99 (20.1)            | 54 (11.0)             |
| Non-DM         | 110               | 81 (73.6)               | 21 (19.1)            | 8 (7.3)               |

**Table 6** Multinomial logistic regression model (treatment success as basis for comparison) used to assess factors associated with outcome of treatment in 766 incident TB patients diagnosed in 2008–2009

|                                         | Died<br>RRR (95%CI) | Failed or lost<br>to follow-up<br>RRR (95%CI) |
|-----------------------------------------|---------------------|-----------------------------------------------|
| DM status*                              |                     |                                               |
| DM-p4p                                  | Reference           | Reference                                     |
| → DM-non-p4p                            | 1.79 (1.05–3.04)    | 1.02 (0.58–1.80)                              |
| Non-DM                                  | 1.69 (0.84–3.40)    | 0.61 (0.25–1.50)                              |
| Sex                                     |                     |                                               |
| Male                                    | 0.80 (0.53–1.24)    | 0.92 (0.54–1.54)                              |
| Female                                  | Reference           | Reference                                     |
| Age, years                              |                     |                                               |
| <60                                     | Reference           | Reference                                     |
| → 60–69                                 | 2.98 (1.47–6.05)    | 0.95 (0.51–1.77)                              |
| ≥70                                     | 7.01 (3.84–12.78)   | 0.85 (0.49–1.47)                              |
| Complication/comorbidities <sup>†</sup> |                     |                                               |
| Any                                     | 1.22 (0.81–1.83)    | 0.91 (0.56–1.48)                              |
| No                                      | Reference           |                                               |

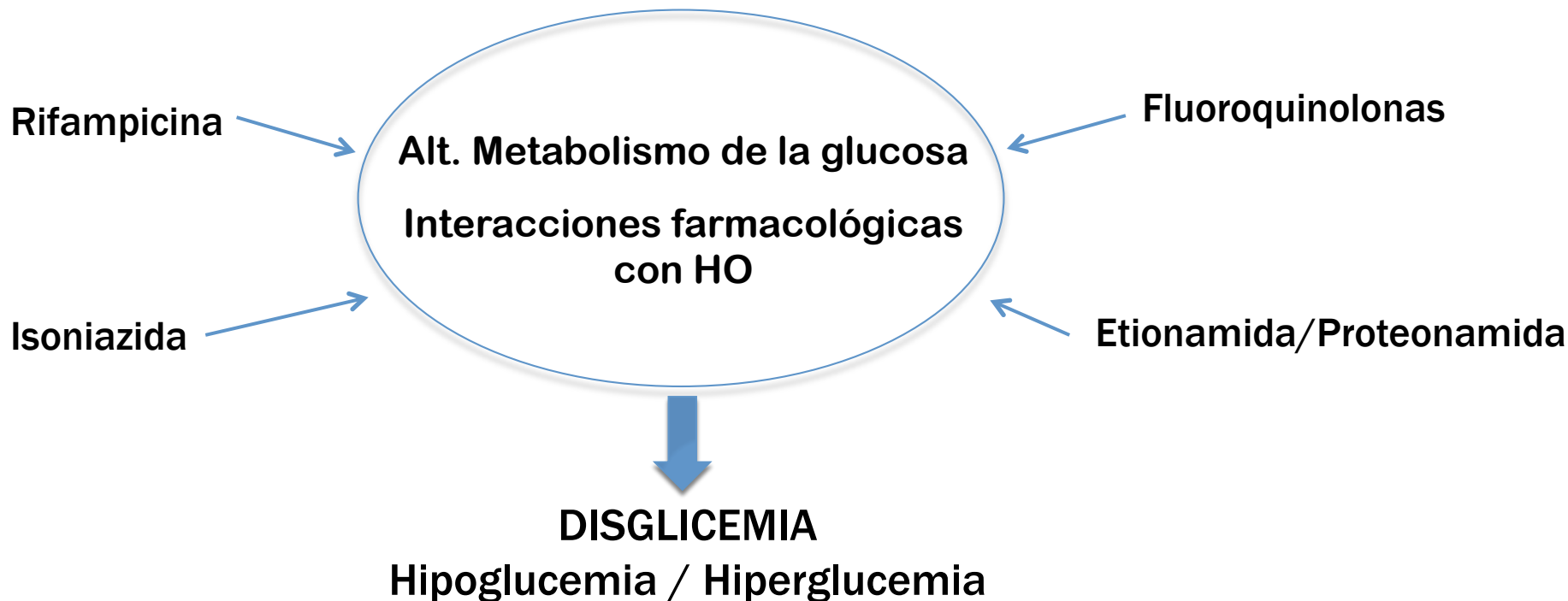
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<sup>†</sup> Included retinopathy, nephropathy, neuropathy, peripheral vascular disease, cardiovascular disease and cerebrovascular disease.

TB = tuberculosis; RRR = relative risk ratio; CI = confidence interval; DM = diabetes mellitus.

# CUAL ES EL MEJOR TRATAMIENTO?

- No existe consenso respecto al mejor Tx
- Tratamiento anti-tuberculosis causa alteraciones de la glucosa



# DISGLICEMIA Y FLUOROQUINOLONAS

## Hipoglicemia

- **Efecto similar sulfonilureas**
  - **↑ liberación de insulina**
- **Interacciones farmacológicas**
  - **Sulfonilureas**
  - **Meglitinidas**
  - **Tioazolidindionas**
- **Interacción con isoenzima P450**

## Hiperglicemia

- **Mecanismo no establecido**
- **↓ liberación de insulina?**

# Risk of Severe Dysglycemia Among Diabetic Patients Receiving Levofloxacin, Ciprofloxacin, or Moxifloxacin in Taiwan

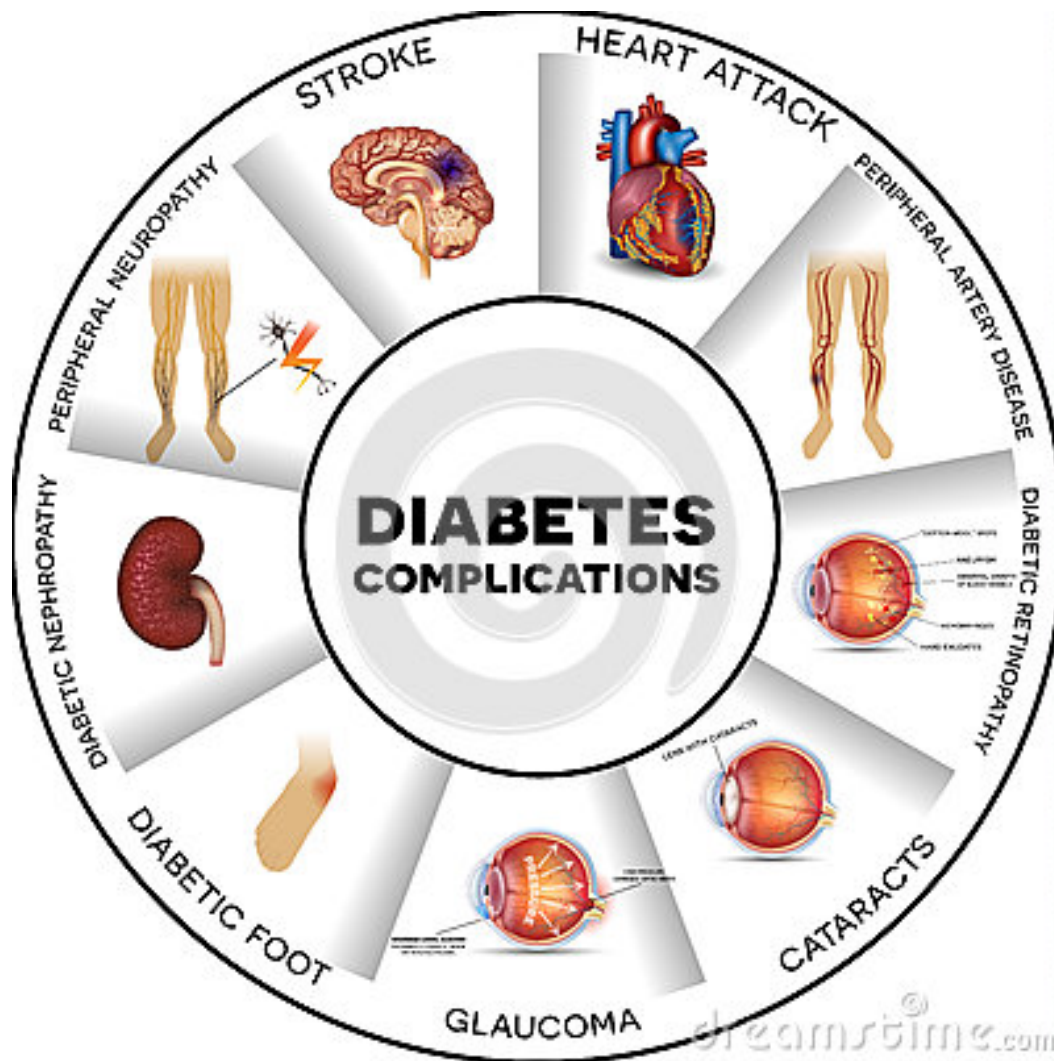
- **Objetivo:** Investigar el riesgo de alteraciones en la glucosa asociado al uso de fluoroquinolonas en pacientes con DM
- **Población en estudio:** 78,433
- **Pacientes solo con Tx VO**
- **Sin otra enfermedad crónica asociada**

**Table 2. Risk of Hyperglycemia and Hypoglycemia Associated With Antibiotic Use in Each Group of Antibiotics**

| Antibiotic Group     | No.    | Events | Incidence (‰) | Time to Event, d,<br>Mean ± SD | Crude OR (95% CI) | Adjusted OR (95% CI) |
|----------------------|--------|--------|---------------|--------------------------------|-------------------|----------------------|
| <b>Hyperglycemia</b> |        |        |               |                                |                   |                      |
| Macrolides           | 29 565 | 48     | 1.62          | 7.92 ± 9.46                    | 1.00              | 1.00                 |
| Cephalosporins       | 20 317 | 42     | 2.07          | 8.17 ± 9.23                    | 1.27 (.84–1.93)   | 1.36 (.87–2.13)      |
| Moxifloxacin         | 4221   | 29     | 6.87          | 3.90 ± 7.20                    | 4.25 (2.68–6.75)  | 2.48 (1.50–4.12)     |
| Levofloxacin         | 11 766 | 46     | 3.91          | 6.22 ± 8.49                    | 2.41 (1.61–3.62)  | 1.75 (1.12–2.73)     |
| Ciprofloxacin        | 12 564 | 50     | 3.98          | 5.60 ± 8.12                    | 2.46 (1.65–3.65)  | 1.87 (1.20–2.93)     |
| <b>Hypoglycemia</b>  |        |        |               |                                |                   |                      |
| Macrolides           | 29 565 | 110    | 3.72          | 6.32 ± 6.81                    | 1.00              | 1.00                 |
| Cephalosporins       | 20 317 | 65     | 3.20          | 7.72 ± 9.83                    | 0.90 (.63–1.17)   | 0.94 (.68–1.32)      |
| Moxifloxacin         | 4221   | 42     | 9.95          | 7.02 ± 9.51                    | 2.69 (1.88–3.85)  | 2.13 (1.44–3.14)     |
| Levofloxacin         | 11 766 | 109    | 9.26          | 7.12 ± 8.48                    | 2.50 (1.92–3.27)  | 1.79 (1.33–2.42)     |
| Ciprofloxacin        | 12 564 | 99     | 7.88          | 9.16 ± 9.40                    | 2.12 (1.62–2.79)  | 1.46 (1.07–2.00)     |

# RECOMENDACIONES

- **Se sugiere:**
  - **Reforzar dieta y modificaciones al estilo de vida**
  - **Evitar el uso de sulfonilureas**
  - **Uso de Metformin e insulina**



## DEFINICIÓN

- Enfermedad renal crónica (ERC) es la disminución de la función renal, expresada por una tasa de filtración glomerular (TFG)  $<60 \text{ ml/min/1.73m}^2$  o como la presencia de daño renal (alteraciones histológicas, albuminuria-proteinuria, alteraciones del sedimento urinario o alteraciones en pruebas de imagen) de forma persistente durante al menos 3 meses.

# Epidemiología de la insuficiencia renal crónica en México

- Incidencia estimada de ERC 377/1,000,000 hab
- Aprox. 52.000 pacientes en terapias sustitutivas
- 80% atendidos en el IMSS

**Tabla 1**

Aspectos epidemiológicos generales de la población

| Variable                 | Diálisis peritoneal<br>N = 20.702 | Hemodiálisis<br>N = 11.010 | Total<br>N = 31.712 |
|--------------------------|-----------------------------------|----------------------------|---------------------|
| Adultos                  | 19.439                            | 10.921                     | 30.360 (96%)        |
| Varones                  | 10.265                            | 5.600                      | 15.865              |
| Mujeres                  | 9.174                             | 5.321                      | 14.495              |
| Pediátricos              | 1.263                             | 89                         | 1.352 (4%)          |
| Varones                  | 626                               | 64                         | 690                 |
| Mujeres                  | 637                               | 25                         | 662                 |
| Grupos de edad (años)    | 61 (rango: 10-81)                 | 59 (rango: 18-84)          | 60 (rango: 10-84)   |
| < 10                     | 62 (0,3%)                         | 0 (0%)                     | 62 (0,2%)           |
| 10 a 19                  | 1.201 (5,8%)                      | 89 (0,8%)                  | 1.290 (4%)          |
| 20 a 29                  | 2.107 (10,2%)                     | 1.547 (14%)                | 3.654 (11,5%)       |
| 30 a 39                  | 2.971 (14,4%)                     | 1.298 (11,8%)              | 4.269 (13,5%)       |
| 40 a 49                  | 4.692 (22,6%)                     | 2.329 (21,2%)              | 7.021 (22%)         |
| 50 a 59                  | 4.351 (21%)                       | 2.175 (19,8%)              | 6.526 (21%)         |
| 60 a 69                  | 3.893 (18,8%)                     | 2.882 (26,2%)              | 6.775 (21%)         |
| 70 a 79                  | 1.311 (6,3%)                      | 597 (5,4%)                 | 1.908 (6%)          |
| > 80                     | 114 (0,6%)                        | 93 (0,8%)                  | 207 (0,7%)          |
| Causas de IRC (%)        | —                                 | —                          | Promedio (%)        |
| Diabetes mellitus        | 43                                | 54                         | 48,5                |
| Hipertensión arterial    | 17                                | 21                         | 19                  |
| Glomerulopatías crónicas | 14,4                              | 11                         | 12,7                |
| No determinada           | 9,2                               | 5,6                        | 7,4                 |
| Riñones poliquísticos    | 4,7                               | 4,3                        | 4,5                 |
| Malformaciones           | 4                                 | 2,1                        | 3                   |
| urinarias congénitas     |                                   |                            |                     |
| Nefropatía lúpica        | 3,3                               | 1,2                        | 2,2                 |
| Nefropatía               | 1,3                               | 0,4                        | 0,85                |
| tubulointersticial       |                                   |                            |                     |
| Litiasis urinaria        | 1,2                               | 0,3                        | 0,75                |
| Vasculares               | 1                                 | 0,1                        | 0,55                |
| Infecciosas              | 0,6                               | 0                          | 0,3                 |
| Nefropatías tóxicas      | 0,3                               | 0                          | 0,2                 |
| Tipo de acceso vascular  |                                   |                            |                     |
| Temporal                 | 77%                               |                            |                     |
| Semipermanente           |                                   | 8%                         | —                   |
| Definitivo (FAVI)        | —                                 | 15%                        |                     |

FAVI: fístula arteriovenosa interna; IRC: insuficiencia renal crónica.

**TABLE 1**

Incidence and relative risk of active tuberculosis (TB) for selected risk factors

|                                | Incidence <sup>#</sup> | Relative disease risk |
|--------------------------------|------------------------|-----------------------|
| <b>Recent TB infection</b>     |                        |                       |
| Infection <1 yr past           | 12.9                   |                       |
| Infection 1–7 yrs past         | 1.6                    |                       |
| <b>Old TB scar</b>             | 2.0–13.6               |                       |
| <b>HIV infection</b>           | 35.0–162               |                       |
| <b>Injection drug use</b>      |                        |                       |
| HIV seropositive               | 76.0                   |                       |
| Other                          | 10.0                   |                       |
| <b>Smoking</b>                 |                        |                       |
| Current smokers                |                        | 2.63                  |
| Ex-smokers                     |                        | 1.41                  |
| Never smokers                  |                        | 1.00                  |
| <b>Passive smoking</b>         |                        | 1.49                  |
| <b>Body mass index</b>         |                        |                       |
| ≥30                            |                        | 0.38                  |
| 25 to <30                      |                        | 0.58                  |
| 23 to <25                      |                        | 0.74                  |
| 18.5 to <23                    |                        | 1.00                  |
| <18.5                          |                        | 2.11                  |
| <b>Silicosis</b>               | 68                     | 30                    |
| <b>DM</b>                      |                        |                       |
| DM <i>versus</i> no DM         |                        | 1.8–4.1               |
| HBA1c ≥7% <i>versus</i> <7%    |                        | 3.1                   |
| <b>Chronic renal failure</b>   |                        | 10.0–25.3             |
| <b>Gastrectomy</b>             |                        | 2–5                   |
| <b>Jejunioileal bypass</b>     |                        | 27–63                 |
| <b>Renal transplant</b>        |                        | 37                    |
| <b>Heart transplant</b>        |                        | 20–74                 |
| <b>Head and neck carcinoma</b> |                        | 16                    |

DM: diabetes mellitus. <sup>#</sup>: among tuberculin-positive subjects per 1,000 person-yrs.

**TABLE 1. Review of the literature regarding TB in patients with chronic renal insufficiency and on dialysis**

| References | Year of publication | Renal treatment           | Country      | Total number of dialysis/CRI patients studied | Number of patients with TB | Prevalence/incidence (%) <sup>a</sup>         | No. of patients with extrapulmonary lesions | Mantoux positive, N (%) | Gender (male/female) | Outcome (died)                           |
|------------|---------------------|---------------------------|--------------|-----------------------------------------------|----------------------------|-----------------------------------------------|---------------------------------------------|-------------------------|----------------------|------------------------------------------|
| 2          | 1974                | HD (+3 PD)                | US           | 136                                           | 5                          | 3.7% over 6 years                             | 3 (60%)                                     | 3 (60%)                 | NA                   | 1 (20%)                                  |
| 3          | 1979                | HD                        | US           | 180                                           | 8                          | 3%/year                                       | 7 (87.5%)                                   | 5 (62.5%)               | 6/2                  | 3 (37.5%)                                |
| 4          | 1979                | HD                        | Japan        | 367                                           | 12                         | 3.3% over 9 years                             | 10 (83.3%)                                  | NA                      | 8/4                  | 9 (75%)                                  |
| 6          | 1988                | HD                        | US           | 172                                           | 10                         | 5.8% over 10 years                            | 4 (49%)                                     | 5 of 9 (55%)            | 6/4                  | 2 (20%) (non-TB)                         |
| 7          | 1980                | HD + CRI                  | US           | 885 on dialysis + unknown CRI                 | 9 on dialysis and 8 CRI    | 10% over 8 years                              | 56% of dialysis patients                    | 9 of 15 (60%)           | 11/6                 | 8 total (47%): 3 (17%) TB; 5 (29) non-TB |
| 8          | 1981                | HD                        | India        | 150                                           | 20                         | 13% over 5 years                              | 8 (40%)                                     | NA                      | 15/5                 | 12 (60%): 2 TB, 10 non-TB                |
| 9          | 1981                | Dialysis                  | Italy        | 300                                           | 7                          | 2.3% over 3 years                             | NA                                          | NA                      | NA                   | NA                                       |
| 10         | 1982                | HD and PD                 | Canada       | 443                                           | 7                          | 1.6% over 13 years                            | 3 (43%)                                     | 2 (29%)                 | 4/3                  | 4 (57%), all non-TB                      |
| 11         | 1990                | HD                        | Saudi Arabia | 205                                           | 23                         | 11% over 9 years                              | 18 (78%)                                    | 61%                     | 6/17                 | 0 (0%)                                   |
| 12         | 1990                | Dialysis                  | Saudi Arabia | 1450                                          | 64                         | 4.4%                                          | 71.8% (in 45.9% of lymphadenopathy)         | NA                      | 37/27                | 1                                        |
| 13         | 1991                | Dialysis                  | UK           | 209 (26 Asian)                                | 8 (all Asian)              | 3.8% over 2 years (31% Asian)                 | 7 extrapulmonary (87%)                      | NA                      |                      | 2 (25%)                                  |
| 14         | 1991                | HD (one on CIPD)          | Saudi Arabia | 26                                            | 7                          | 28% over 11 years                             | 5 (57%)                                     | 40%                     | 2/5                  | 0 (0%)                                   |
| 15         | 1995                | HD                        | Spain        | 158                                           | 7                          | 4.4% over 15 years                            | 5 (71.4%)                                   | “Not helpful”           | NA                   | 0 (0%)                                   |
| 16         | 1996                | HD                        | Jordan       | 927                                           | 11                         | 1.2% over 7 years                             | 9 (81.8%)                                   | 2 of 6 (33.3%)          | 4/7                  | 5 (due to non-TB causes)                 |
| 17         | 1996                | HD                        | Turkey       | 110                                           | 26                         | 23.6%                                         | 8 (30%)                                     | 0 (0%)                  | 20/6                 | 0 (0%)                                   |
| 18         | 1997                | HD                        | Saudi Arabia | 270                                           | 13                         | 4.8% over 7 years                             | 5/13 (38%)                                  | 0 (0%)                  | 3/10                 | 0                                        |
| 19         | 1997                | ?                         | US (Texas)   |                                               | 10                         | 10 patients over 11 years                     | 7 (70%)                                     | NA                      | 6/4                  | 2 (20%)                                  |
| 20         | 1997                | HD                        | Poland       | 188                                           | 11                         | 5.8% over 7 years                             | 6 (54.5%)                                   | NA                      | 4/7                  | 1 (9%)                                   |
| 21         | 1998                | HD and CAPD               | Canada       | 813                                           | 9                          | Incidence: 253/100,000                        | NA                                          | NA                      | NA                   | NA                                       |
| 22         | 1999                | HD                        | Saudi Arabia | 210                                           | 17                         | 8.1% over 5 years                             | 8 (47%)                                     | 9/15 (60%)              | 9/8                  | 0?                                       |
| 23, 24     | 1999                | CRI (not yet on dialysis) | Saudi Arabia | 80                                            | 8                          | 10% over 3 years                              | 4/8 (50%)                                   | 8 positive (100%)       | 3/5                  | 0 (0%)                                   |
| 25         | 1999                | PD (children)             | Turkey       | 70                                            | 4                          | 5.7% over 8 years                             | 1 (25%)                                     | NA                      |                      | 2 (50%)                                  |
| 26         | 2000                | HD                        | Turkey       | 296                                           | 18                         | 6.08% over 16 years                           | 7/18 (38%)                                  | 2 (11.1%)               | 9/9                  | 4 (22%)                                  |
| 27         | 2000                | HD                        | Yugoslavia   | 219                                           | 9                          | 4.1% over 8 years                             | NA                                          | NA                      | NA                   | 0 (0%)                                   |
| 28         | 2001                | HD                        | Taiwan       | 24,553                                        | 122                        | Incidence: 493.4/100,000 (1997)               | 51%                                         | NA                      | 64/58                | TB 3 (1.7%), non-TB 43 (25.6%) (x3.3)    |
| 29         | 2001                | CAPD                      | Hong Kong    | 790                                           | 38                         | 4.8% over 6 years                             | 20 (53%)                                    | NA                      | 18/20                | 11 (29%)                                 |
| 30         | 2001                | HD                        | Turkey       | 157                                           | 9                          | Incidence: 1910 per 100,000; prevalence: 5.7% | 5 (55%)                                     | “Low rate”              | 6/3                  | 1 (11%)                                  |
| 31         | 2002                | HD and CAPD               | UK           | 431                                           | 11                         | 11 of 431 over 5 years                        | 5 (45%)                                     | NA                      | NA                   | 2 (18%)                                  |

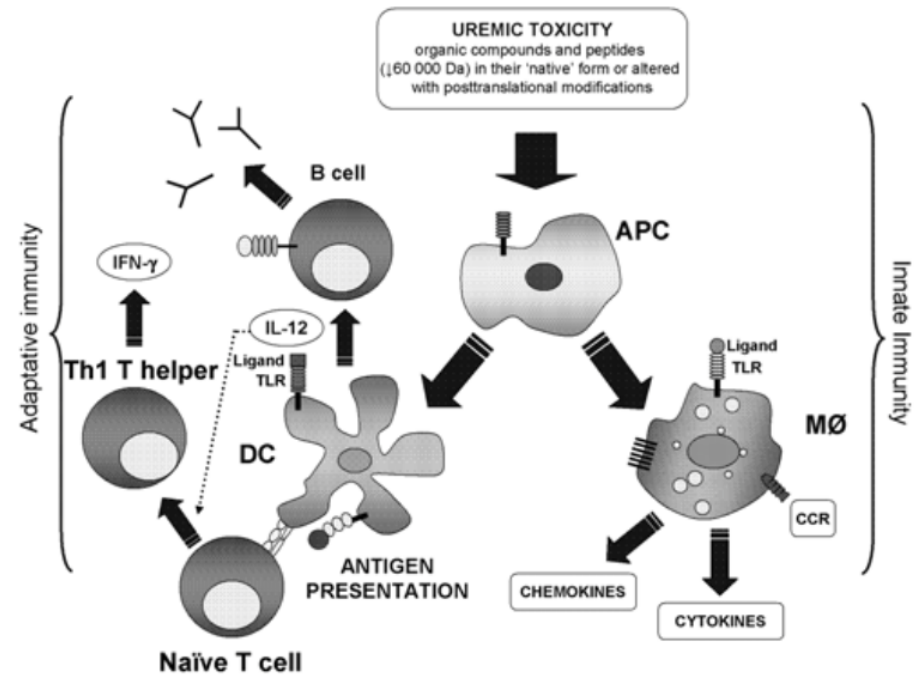
HD, hemodialysis; CRI, chronic renal insufficiency, not yet on dialysis; PD, peritoneal dialysis; CIPD, chronic intermittent peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; prevalence, number of new and existing cases in the population during a time period; incidence, number of new cases in the population during a time period (1 year); NA, not available; TB, direct TB-related death; non-TB, not TB-related death.

<sup>a</sup> If not mentioned otherwise, the numbers in this column refer to prevalence.

# COMO AFECTA LA IRC LA TUBERCULOSIS?

## ■ Uremia

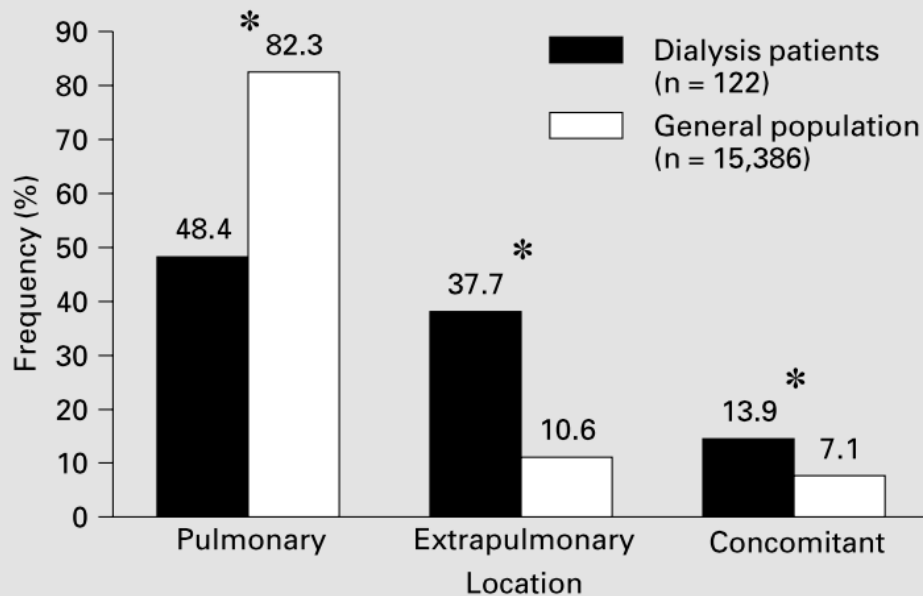
- ↓ Numero de Linfocitos
- Disbalance Th1/Th2
- Función celular alterada
- Déficit de Vitamina D



# COMO MODIFICA LA IRC LA TUBERCULOSIS?

- **Sx constitucional INSIDIOSA**
  - Fiebre
  - Anorexia
  - Perdida de peso
- **< Sx Respiratoria (tos, expectoración, hemoptisis)**
- **> TB EXTRAPULMONAR**

# Tuberculosis in Maintenance Dialysis Patients



**Fig. 2.** Location of TB in dialysis patients and the general population. The proportions were examined by  $\chi^2$  test. \*  $p < 0.05$ .

- 1997 : 15,508 pacientes con TB
- 122 pacientes con IRC en diálisis
- Mediana de tiempo entre inicio de Terapia sustitutiva y Dx de TB: 11 meses (rango 0 – 146)

|                      |    |      |
|----------------------|----|------|
| Lymphadenitis        | 13 | 40.6 |
| Bone and joint       | 4  | 12.5 |
| Genitourinary system | 4  | 12.5 |
| Meningitis           | 1  | 3.1  |
| Digestive system     | 2  | 6.3  |
| Skin and eye         | 0  | 0.0  |
| Other organ          | 8  | 25.0 |

**Cuadro 3. Clasificación de la enfermedad renal crónica de acuerdo a la TFG y el daño renal.**

| <b>ESTADIO</b> | <b>DESCRIPCIÓN</b>                                              | <b>Tasa de Filtración Glomerular (mL/min/1.73m<sup>2</sup>)</b> | <b>PLAN DE ACCIÓN</b>                                                                                                                                                     |
|----------------|-----------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | Incremento del Riesgo                                           | ≥90<br>(con factores de riesgo)                                 | Escrutinio y reducción de factores de riesgo para ERC                                                                                                                     |
| 1              | Daño renal con Tasa de Filtrado Glomerular normal               | ≥ 90                                                            | Diagnóstico y tratamiento; tratamiento de morbilidad asociada; intervenciones para retardar la progresión; reducción de factores de riesgo para enfermedad cardiovascular |
| 2              | Daño renal con Tasa de Filtrado Glomerular levemente disminuida | 60-89                                                           | Estimación y retraso de la progresión                                                                                                                                     |
| 3              | Moderada disminución de la Tasa de Filtrado Glomerular          | 30-59                                                           | Evaluación y tratamiento de complicaciones                                                                                                                                |
| 4              | Severa disminución de la Tasa de Filtrado Glomerular            | 15-29                                                           | Preparar para terapia de reemplazo renal                                                                                                                                  |
| 5              | Enfermedad renal terminal                                       | < 15<br>(o diálisis)                                            | Terapia de reemplazo renal (si hay uremia)                                                                                                                                |

Modificada de: Levey A. *Ann Intern Med* 2004; 141: 959-961

# TRATAMIENTO DE TB E IRC

**Table 4** Recommended doses of first-line drugs in chronic kidney disease (CKD)

|               | Stage 1–3 CKD*                               | Stage 4 and 5 CKD*, †                          | Renal transplant recipients                  |
|---------------|----------------------------------------------|------------------------------------------------|----------------------------------------------|
| Isoniazid     | 300 mg daily                                 | 300 mg daily<br>or 15 mg/kg max 900 mg 3×/week | 300 mg daily                                 |
| Rifampicin    | <50 kg: 450 mg daily<br>≥50 kg: 600 mg daily | <50 kg: 450 mg daily<br>≥50 kg: 600 mg daily   | <50 kg: 450 mg daily<br>≥50 kg: 600 mg daily |
| Pyrazinamide‡ | <50 kg: 1.5 g daily<br>≥50 kg: 2 g daily     | 25–30 mg/kg 3×/week                            | <50 kg: 1.5 g daily<br>≥50 kg: 2 g daily     |
| Ethambutol§   | 15 mg/kg daily                               | 15–25 mg/kg 3×/week (max 2.5 g)                | 15 mg/kg daily                               |
| Moxifloxacin  | 400 mg daily                                 | Not suitable for 3× weekly regimen             | 400 mg daily                                 |

Isoniazid and rifampicin may be given intravenously where absorption is compromised. Dose: Isoniazid 300 mg as single daily dose; rifampicin 450 mg or 600 mg depending on weight by infusion over 2–3 h.

\*See box 1.

†Also applies to dialysis.

‡Check uric acid and monitor for gout.

§Check baseline colour vision and visual acuity and warn patients to report any changes in red/green discrimination or visual acuity. Check peak and trough drug levels.

# TRATAMIENTO DE TB E IRC

**Table A1** Second-line drugs in chronic kidney disease (CKD)

| Chronic kidney disease                                                     |              |                                                    |                                                          |
|----------------------------------------------------------------------------|--------------|----------------------------------------------------|----------------------------------------------------------|
| Drug                                                                       | GFR (ml/min) | Dose                                               | Dialysis                                                 |
| Streptomycin*                                                              | 20–50        | 50–100% daily (7.5–15 mg/kg every 24 h)            | HD as for GFR <10 ml/min<br>CAVH as for GFR 10–20 ml/min |
|                                                                            | 10–20        | 50–100% every 24–72 h (7.5–15 mg/kg every 24–72 h) |                                                          |
|                                                                            | <10          | 50–100% every 72–96 h (7.5–15 mg/kg every 72–96 h) |                                                          |
| PAS (manufacturer states “avoid in severe renal failure”)                  | >50 ml/min   | 100%                                               | HD: give after HD                                        |
|                                                                            | 10–50        | 50–75%†                                            | PD: as <10 ml/min                                        |
|                                                                            | <10          | 50%†                                               | CAVH: as <10 ml/min                                      |
| Ethionamide‡                                                               | >50          | No change                                          | No changes in HD                                         |
|                                                                            | 10–50        | No change                                          |                                                          |
|                                                                            | <10          | 50%                                                |                                                          |
| Capreomycin§ (adjust dose to give steady state concentrations of 10 µg/ml) | >50          | 24 h dose interval                                 | HD: give after HD                                        |
|                                                                            | 10–50        | 48 h dose interval¶                                | PD: no change                                            |
|                                                                            | <10          | 48 h dose interval¶                                | CAVH: dose as 10–50 ml/min                               |
| Cycloserine** (blood monitoring levels <30 mg/l)                           | >50          | 12 h dose interval                                 | HD: no change                                            |
|                                                                            | 10–50        | 12–24 h                                            | PD: no change                                            |
|                                                                            | <10          | 24 h                                               | CAVH: dose as 10–50 ml/min                               |

\*Intramuscular: 15 mg/kg (max 1 g daily). Dose is reduced in <50 kg and >40 years to max 500–750 mg daily or 12–15 mg/kg 2–3 times/week. Peak plasma concentrations of streptomycin should be between 15 and 40 µg/ml and trough concentrations <3–5 µg/ml or <1 µg/ml in CKD or those >50 years.

†Caution when reducing dose of PAS (may become subtherapeutic). Usual adult dose 4 g three times a day. ATS recommend 4 g twice daily if creatinine clearance <30 ml/min. Granules should be administered in acidic food or drink with a pH<5 (eg, fruit juice) and should be swallowed without chewing.

‡Adults 15–20 mg/kg/day in single or divided doses (usual dose 500 mg–1 g daily). ATS recommend 250–500 mg daily.

§Adults 1 g intramuscular every 24 h (not to exceed 20 mg/kg/day) ¶or 3 times/week. Do therapeutic drug monitoring.

\*\*Usual adult dose 500 mg–1 g daily in divided doses, monitored by therapeutic drug monitoring. The initial adult dosage most frequently given is 250 mg twice daily at 12 h intervals for the first 2 weeks. In severe CKD, 500 mg 3 times/week. A daily dosage of 1 g should not be exceeded. Careful monitoring for evidence of neurotoxicity.

CAVH, continuous arteriovenous haemodialysis; GFR, glomerular filtration rate; HD, haemodialysis; PAS, para-amino salicylic acid; PD, peritoneal dialysis.

TABLE 7.1 Adjustment of anti-TB drugs in renal insufficiency<sup>a</sup>

| DRUG                                  | RECOMMENDED DOSE AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30 ML/MIN OR FOR PATIENTS RECEIVING HAEMODIALYSIS (UNLESS OTHERWISE INDICATED DOSE AFTER DIALYSIS)     |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Isoniazid                             | No adjustment necessary                                                                                                                                                       |
| Rifampicin                            | No adjustment necessary                                                                                                                                                       |
| Pyrazinamide                          | 25–35 mg/kg per dose three times per week (not daily)                                                                                                                         |
| Ethambutol                            | 15–25 mg/kg per dose three times per week (not daily)                                                                                                                         |
| Rifabutin                             | Normal dose can be used, if possible monitor drug concentrations to avoid toxicity.                                                                                           |
| Rifapentine                           | No adjustment necessary                                                                                                                                                       |
| Streptomycin                          | 12–15 mg/kg per dose two or three times per week (not daily) <sup>b</sup>                                                                                                     |
| Capreomycin                           | 12–15 mg/kg per dose two or three times per week (not daily) <sup>b</sup>                                                                                                     |
| Kanamycin                             | 12–15 mg/kg per dose two or three times per week (not daily) <sup>b</sup>                                                                                                     |
| Amikacin                              | 12–15 mg/kg per dose two or three times per week (not daily) <sup>b</sup>                                                                                                     |
| Ofloxacin                             | 600–800 mg per dose three times per week (not daily)                                                                                                                          |
| Levofloxacin                          | 750–1000 mg per dose three times per week (not daily)                                                                                                                         |
| Moxifloxacin                          | No adjustment necessary                                                                                                                                                       |
| Gatifloxacin                          | 400 mg three times a week                                                                                                                                                     |
| Cycloserine                           | 250 mg once daily, or 500 mg/dose three times per week <sup>c</sup>                                                                                                           |
| Terizidone                            | Recommendations not available                                                                                                                                                 |
| Prothionamide                         | No adjustment necessary                                                                                                                                                       |
| Ethionamide                           | No adjustment necessary                                                                                                                                                       |
| Para-aminosalicylic acid <sup>d</sup> | 4 g/dose, twice daily maximum dose <sup>d</sup>                                                                                                                               |
| Bedaquiline                           | No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).                    |
| Delamanid                             | No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).                    |
| Linezolid                             | No adjustment necessary                                                                                                                                                       |
| Clofazimine                           | No adjustment necessary                                                                                                                                                       |
| Amoxicillin/clavulanate               | For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily |
| Imipenem/cilastin                     | For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours                                               |
| Meropenem                             | For creatinine clearance 20–40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours                                              |

# CONCLUSIONES

- La DM es el factor de riesgo mas importante para el desarrollo de tuberculosis en México.
- Los pacientes con DM + TB deben tener un seguimiento estrecho de ambas enfermedades.
- El adecuado control glucémico SI tiene impacto en el desenlace al Tx.
- Se debe **MONITORIZAR** los niveles de glucosa (glucosa y HbA1c)
- EVITAR el uso de HO (sulfonilureas)
- La ERC, trasplante renal **NO SON CONTRAINDICACIONES** para Tx anti-TB de 1ra y/o 2da línea
- **EN TODO PACIENTE**, se debe ajustar el tratamiento al peso y comorbilidades



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