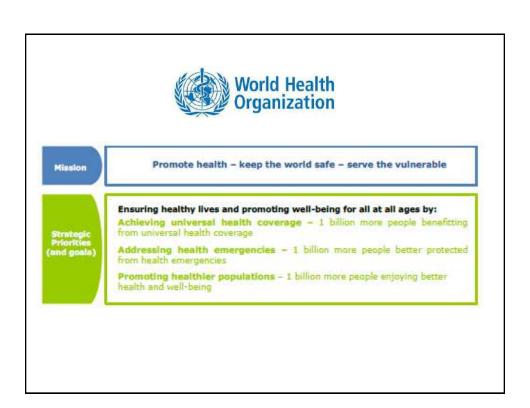
# Reinserting CE and AE in the New NTD roadmap and Universal Health Coverage

 $28^{th}$  World Congress Of Echinococcosis: "Toward the Control and Elimination of Echinococcosis" Centro de Convenciones, Lima  $-\ 29-31$  October, 2019

Dr Bernadette ABELA-RIDDER Department of the Control of Neglected Tropical Diseases





# Universal health coverage (UHC)

<u>all</u> people and communities have access to <u>quality</u> health services they need,

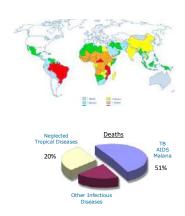
when and where they need them, without financial hardship.

It includes the full range of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care.



## Neglected Tropical Diseases

- · A proxy for poverty and disadvantage
- Preventable yet prevalent
- Affect populations with low visibility & little political voice
- Do not travel widely
- Cause stigma and discrimination, especially of girls and women
- Important impact on morbidity and mortality
- Control challenged by circumstance: elimination possible with effective and feasible solutions
- · Relatively neglected by research
- Ethical responsibility





## **Neglected Tropical Diseases**

A proxy for poverty and disadvantage

## **5 Key Strategies**

- Innovative and intensified disease management
- · Preventive chemotherapy
- · Veterinary public health
- Vector ecology and management
- Water, sanitation and hygiene

## 20 Diseases



World Health Organization

## Neglected tropical Diseases

- NTDs cost developing communities billions of dollars each year in direct health costs, loss of productivity and reduced educational attainment.
- NTDs are a best buy in global public health returns to individuals for every dollar invested in preventive chemotherapy are up to 25 times, given the averted out pocked costs and loss of productivity
- NTDs relate to sustainable development goals in a way that is mutually reinforcing
- Addressing NTDs supports the vision of universal health coverage:
  - NTD programmes reach some of the world's poorest communities and can open up equitable access to care and services for these populations
  - NTDs can serve as a litmus test for UHC, which can only be achieved if people at risk of NTDs have access to health services





## Strategic framework

- Technical progress e.g. scientific understanding, effective intervention
  - Strategy and service delivery e.g. planning and implementation, access and logistics
  - Enablers e.g. advocacy and funding, collaboration and multisectoral action
- B. Crosscutting approaches
- Integrating NTDs on common delivery platforms that combine efforts across multiple diseases
  - Mainstreaming within national health systems to improve the quality of NTD management in the context of UHC
  - Coordinating with other sectors within and beyond health on NTDrelated interventions
- Strengthening country capacity and the provision of global and regional resources and expertise – to support the delivery of NTD interventions
- Country ownership at national and subnational levels
- Clear stakeholder roles across NTD ecosystem
- Organisational setups, operating models and mindsets aligned to deliver on 2030 targets



## Cross-cutting approaches



INTEGRATING...

Programmatic

rogress against

C. Operating

model and culture

...across NTDs: common delivery platforms combining efforts across multiple diseases - 岑 - MAINSTREAMING...

...within national health systems: improving the quality of NTD management in the context of UHC - COORDINATING...

...among ecosystem stakeholders: working with other sectors within and beyond health on NTDrelevant interventions



## -STRENGTHENING HEALTH SYSTEMS...

 $... in-country\ foundational\ systems: improving\ capacity\ to\ deliver\ interventions\ on\ the\ ground\ e.g.\ supply\ chain,\ M\&E$ 

...global and regional resources & expertise: expanding overall support for NTD programmes e.g. advocacy, funding



## Weak data, estimates

#### 111 countries

Endemic for cystic and alveolar echinococcosis

Cystic echinococcosis is spread across all continents except Antarctica

Alveolar echinococcosis is endemic in Asia, Continental Europe and North America

(Cestodes)	FOODBORNE	FOODBORNE	FOODBORNE	FOODBORNE	FOODBORNE
	ILLNESSES	DEATHS	YLDS	YLLS	DALYS
Echinococcus	43 076	482	12 121	27 626	39 950
granulosus	(25 881–371 177)	(150–3 974)	(5 515–99 213)	(8 577–227 715)	(16 996–322 953)
Echinococcus	8 375	7 771	8 749	303 039	312 461
multilocularis	(656–17 005)	(243–15 896)	(856–22 576)	(8 102–622 954)	(9 083–640 716)

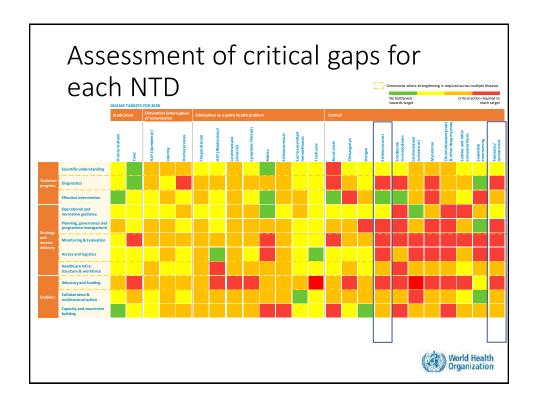
Source: WHO estimates of the global burden of foodborne diseases Foodborne diseases burden epidemiology reference group 2007-2015 http://www.who.int/foodsafety/publications/foodborne\_disease/fergreport/en/

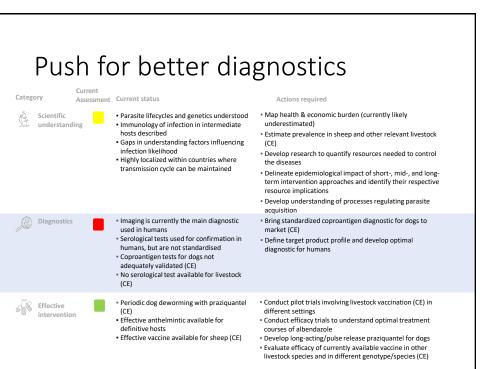
### CE as a public health problem:

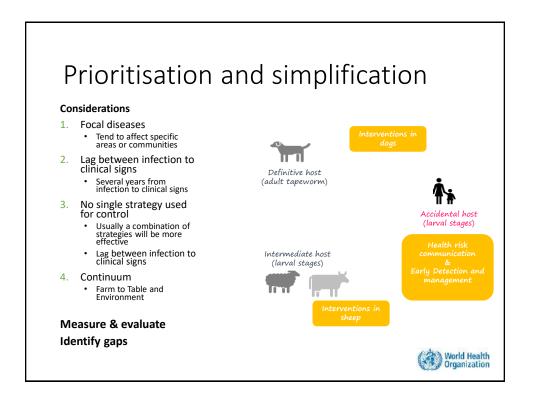
provisionally defined as an estimated 1 case/100,000 people.

### CE hyper endemic area:

provisionally defined as an estimated 100 cases/100,000 people.









# COUNTRY LEVEL: Epidemiological Indicators



## 1. Number of CE cases reported

- Prevalence
- Geographical location
- Age
- 2. Number of CE cases by US in school age children (SAC)
  - Incidence



- 3. % of animals with CE lesions at the abattoir.
  - Only if many of the animals in the region go to abattoir

# COUNTRY LEVEL: Control Indicators





- Number of CE endemic areas
- Number of people at risk of CE
- Outcome #1: % hyperendemic areas\* with control for CE (Geographical coverage)
- Outcome #2: % people at risk of CE living in a control area

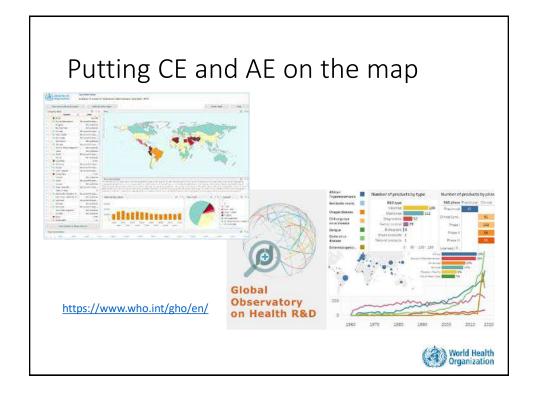
<sup>\*</sup> Provisionally defined as an estimated 100 cases/100,000 people.



## GLOBAL LEVEL: Control Indicators



- Number of CE cases by country
- Number of endemic countries in which CE is a public health problem.
- Number of countries with intensified control in hyperendemic areas



## The manual(s)

• The how to on: Expert Consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans

https://www.who.int/echinococcosis/resources/jactatropica\_200911001/en/

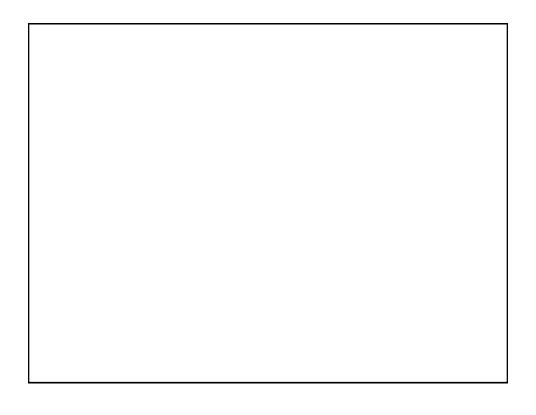
- · Manual based on best evidence and expert opinion
- · Dissemination and training
- · Adaptation by country and setting
- · Templates for data & information gathering

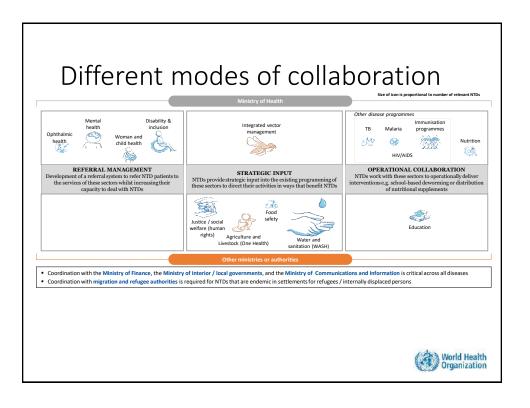


Thanks to Meritxell Donadeu who is assisting WHO on NZDs

Bernadette ABELA-RIDDER Department of the Control of Neglected Tropical Diseases Email: abelab@who.int - Skype: abelaridder







HAZARD	FOODBORNE	FOODBORNE	FOODBORNE
(Cestodes)	ILLNESSES	DEATHS	YLDS
Echinococcus	43 076	482	12 121
granulosus	(25 881–371 177)	(150–3 974)	(5 515–99 213)
Echinococcus	8 375	7 771	8 749
multilocularis	(656–17 005)	(243–15 896)	(856–22 576)
Taenia solium	370 710 (282 937–478 123)	28 114 (21 059–36 915)	1 192 236 (916 049– 1 522 267)



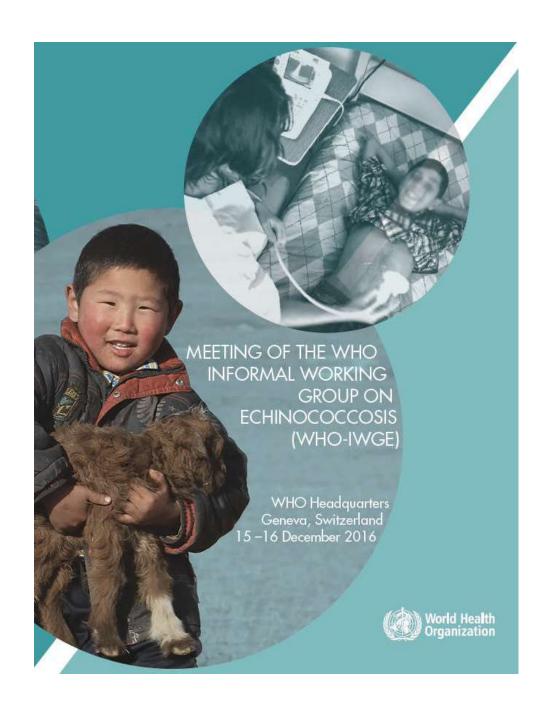
The 'CE Technical Manual': reaching out to health services and patients

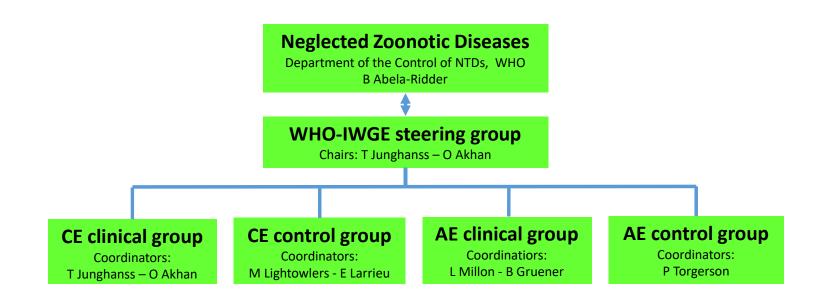
Thomas Junghanss

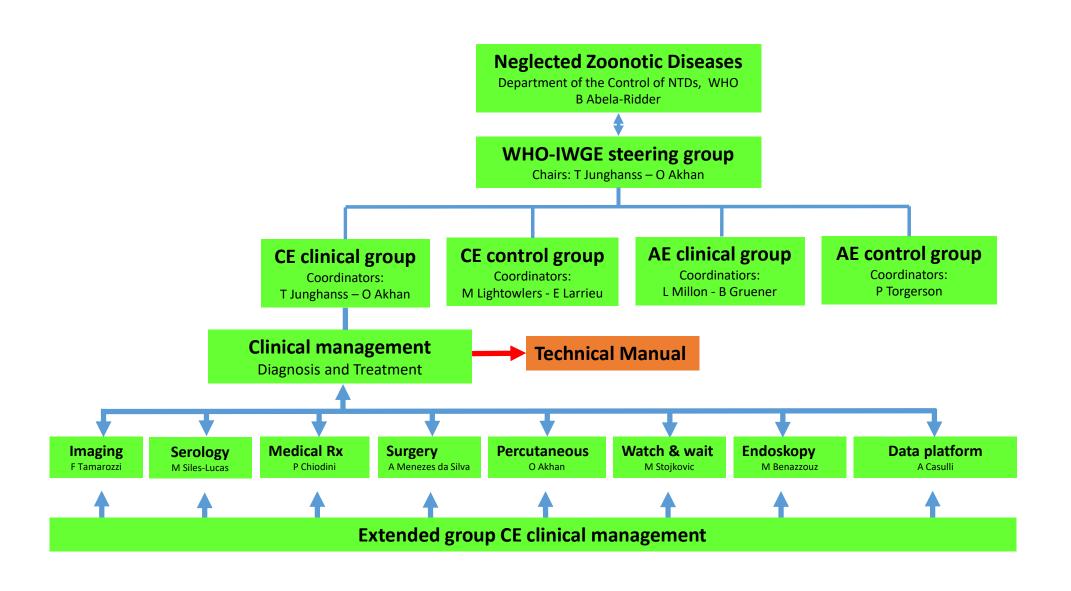
WHO-IWGE

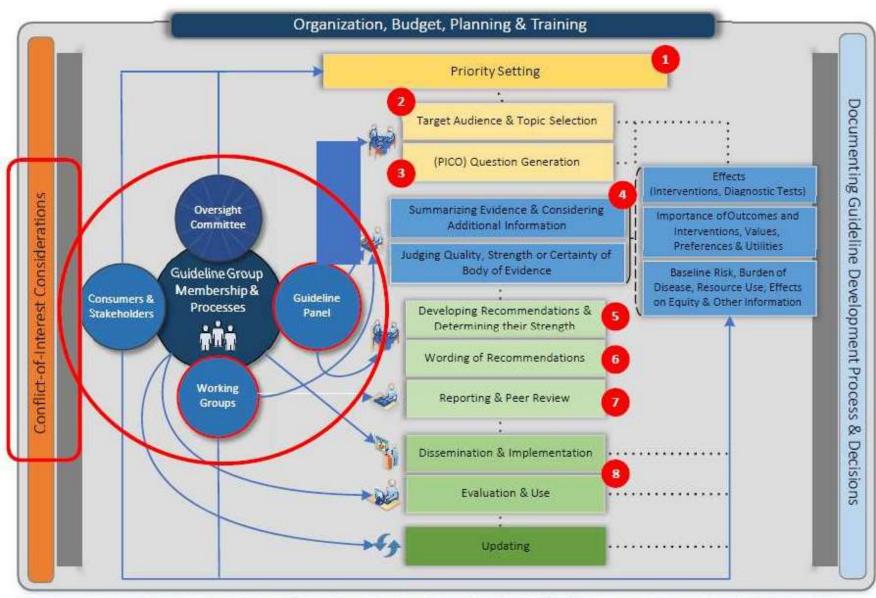
WAE

Lima 2019









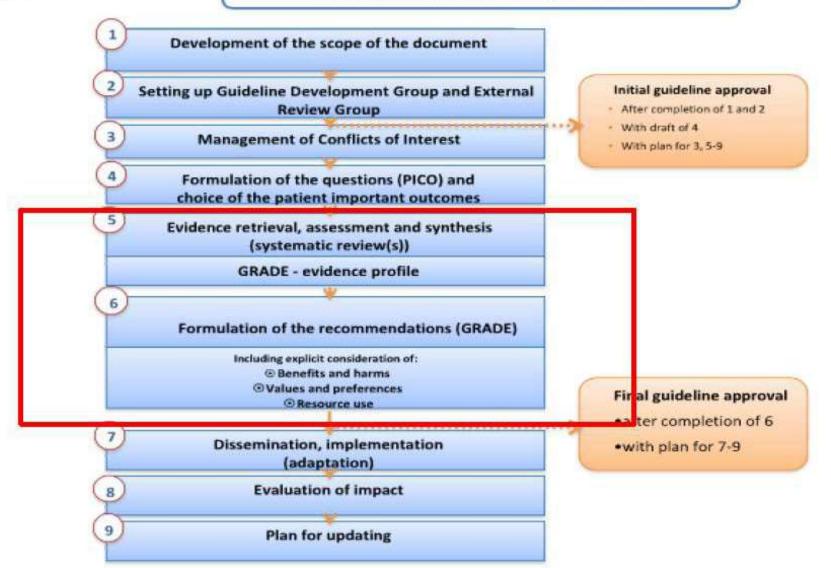
GRADE

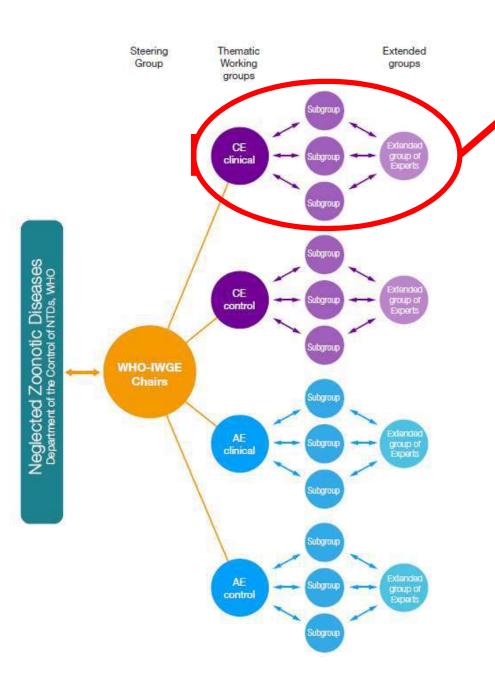
Grading of
Recommendations
Assessment,
Development and
Evaluation

Schünemann et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014 Feb 18;186(3):E123-42. <a href="http://cebgrade.mcmaster.ca/guidecheck.html">http://cebgrade.mcmaster.ca/guidecheck.html</a>



## **Guideline Development Process**





## PICO questions, lit. search, data extraction

Critical ISSUE PICO-question	Title of publication, journal, year	Main findings		
	Publication 1			
Issue 1	Publication 2			

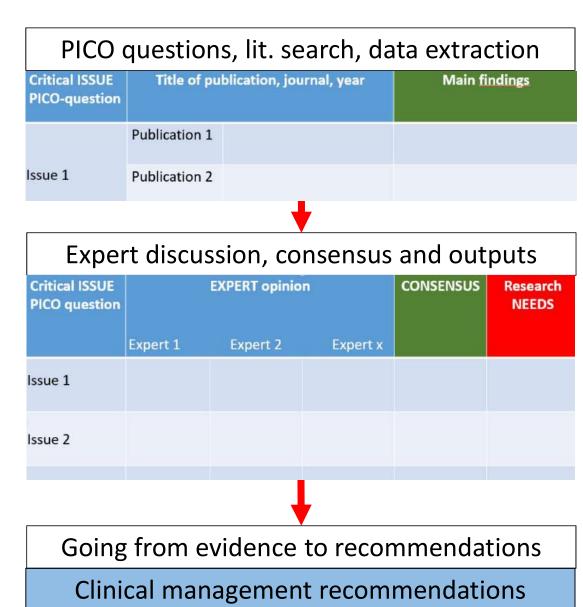
## Expert discussion, consensus and outputs

Critical ISSUE PICO question	EXPERT opinion			CONSENSUS	Research NEEDS
	Expert 1	Expert 2	Expert x		
Issue 1					
Issue 2					

Going from evidence to recommendations

Clinical management recommendations

## **CE Technical Manual**



## STEP 1

Formulation "Critical issues" / PICCO questions, literature search, data extraction

**STEP 1**: Formulation "Critical issues", literature search, data extraction

Critical ISSUE PICO-question	Title of publication, journal, year			Main fi	indings
	Publication 1				
Issue 1	Publication 2				
	Publication 3				
	etc.				
Issue 2					
etc.					

## PICO questions - "Critical issues"

P patient
I intervention
C comparison
O outcome

Each PICO question will result in one recommendation

e.g. Is peri-interventional ABZ reducing post-interventional CE-recurrence?

Patients: patients undergoing PAIR with CE1 and CE3a cysts

Intervention: ABZ

Comparison: Placebo

Outcome: CE recurrence within 5 years

Title of publication	
Journal, year of publication	
<ul><li>Study design</li><li>Study type</li><li>Number of participants enrolled</li></ul>	
Type of intervention Setting of delivery of intervention	
Objective	
Inclusion / exclusion criteria	
Cyst stage documented	
Follow-up - Loss to follow-up	
Types of outcome(s) Outcome 1: etc.	
Outcome 1: - Number included into analysis - Main results	
Strength / limitations	

Title of publication
Journal, year of publication
<ul><li>Study design</li><li>Study type</li><li>Number of participants enrolled</li></ul>
Type of intervention Setting of delivery of intervention
Objective
Inclusion / exclusion criteria
Cyst stage documented
Follow-up - Length of follow-up - Loss to follow-up
Types of outcome(s) Outcome 1: etc.
Outcome 1: - Number included into analysis - Main results
Strength / limitations

Proportion of recurrence

Title of weblingting
Title of publication
Journal, year of publication
<ul><li>Study design</li><li>Study type</li><li>Number of participants enrolled</li></ul>
Type of intervention Setting of delivery of intervention
Objective
Inclusion / exclusion criteria
Cyst stage documented
Follow-up - Loss to follow-up
Types of outcome(s) Outcome 1: etc.
Outcome 1: - Number included into analysis - Main results
Strength / limitations

> 5 years

< 90 %

Proportion of recurrence

Title of publication	
Journal, year of publication	
Study design - Study type - Number of participants enrolled	
Type of intervention Setting of delivery of intervention	
Objective	
Inclusion / exclusion criteria	
Cyst stage documented	
Follow-up - Length of follow-up - Loss to follow-up	
Types of outcome(s) Outcome 1: etc.	
Outcome 1: - Number included into analysis - Main results	
Strength / limitations	

> 5 years

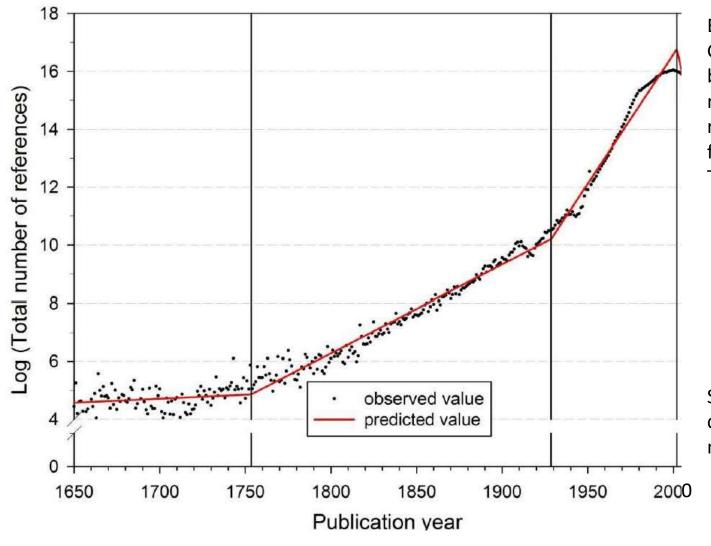
< 90 %

Proportion of recurrence

**Strength** ..... / limitations ....

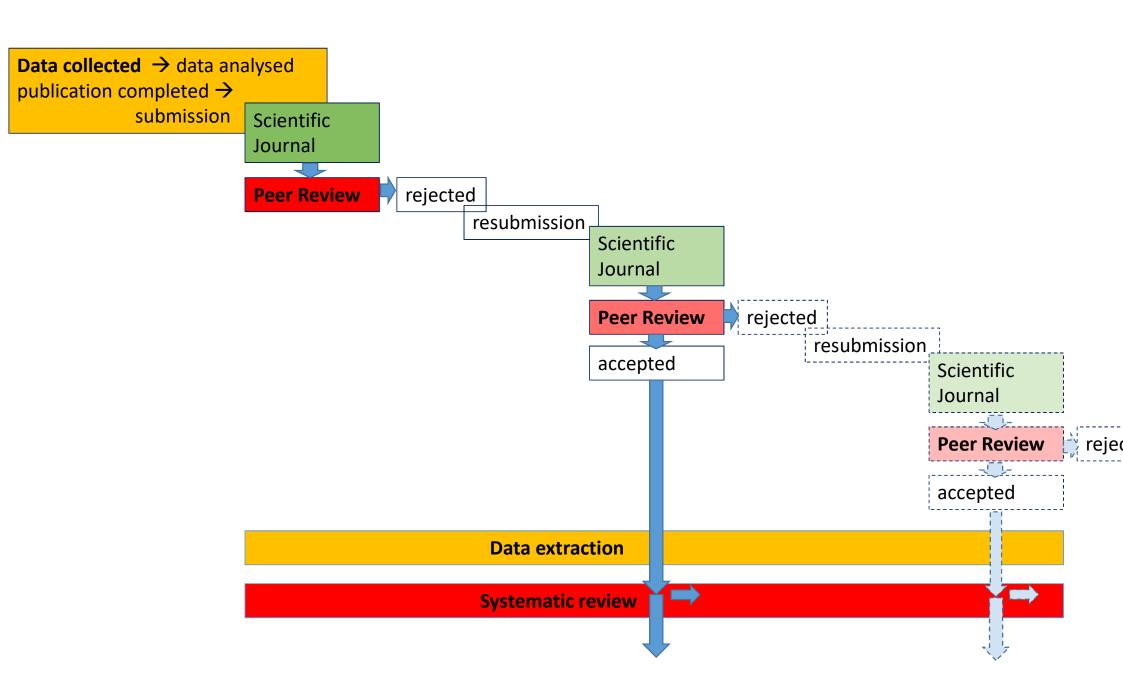
Why is it so difficult these days to get useful robust data /estimates?

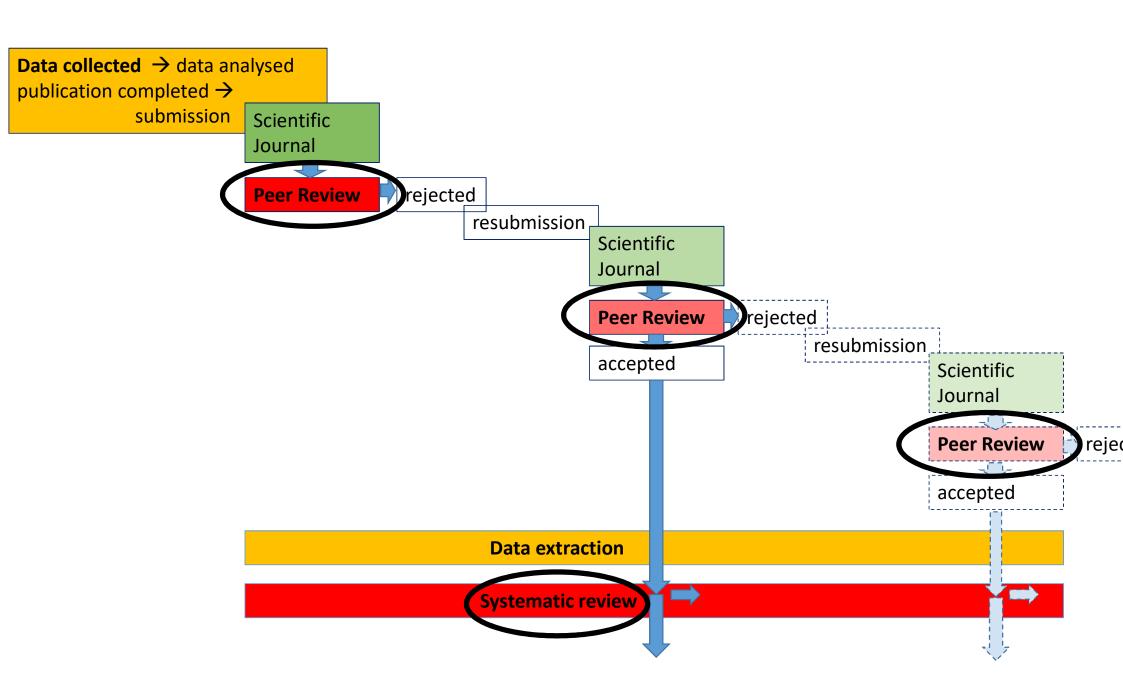
clinical guideline development



Bornmann L, Mutz R (2014)
Growth rates of modern science: A
bibliometric analysis based on the
number of publications and cited
references. Journal of the Association
for Information Science and
Technology

Segmented growth of the annual number of cited references from 1650 to 2012 in the medical and health sciences



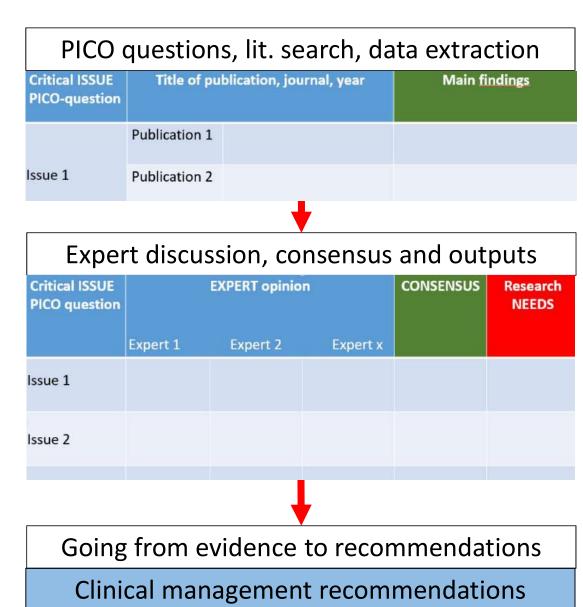


Data extraction to generate the evidence base for an expert consensus and identification of research needs



It may be one of one's own papers that does not make it

## **CE Technical Manual**



# STEP 2

Expert discussion, consensus, outputs

**STEP 2**: Expert discussion, consensus, outputs

Critical ISSUE PICO question	EXPERT opinion			CONSENSUS	Research NEEDS
	Expert 1	Expert 2	Expert x		
Issue 1					
Issue 2					
Issue 3					
Issue x					

# STEP 3

Going form evidence to recommendation

### STEP 3: Going form evidence to recommendation

#### Factors that need to be considered:

- Importance of Problem
- Benefits
- Harms
- Certainty of evidence
- Values and Preferences
- Balance of effects

- Resources required
- · Certainty of resources required
- Cost-Effectiveness
- Equity
- Acceptability
- Feasibility
- Recommendation

## Evidence-based diagnosis and treatment

Infectious Diseases Society of America grading system for ranking recommendations in clinical guidelines

#### Strength of recommendation

Good evidence to support a recommendation for use

Moderate evidence to support a recommendation for use

Poor evidence to support a recommendation

Moderate evidence to support a recommendation against use

Good evidence to support recommendation against use

#### **Quality of evidence**

Α

В

Ш

Evidence from ≥ 1 properly randomized, controlled trail

Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time series; or from dramatic results from uncontrolled experiments

Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees

There is nothing wrong with coming to the conclusion that a diagnostic or treatment approach is rejected

Rejection of an unsafe diagnostic or treatment approach can safe just as many lives as acceptance of a well-proven method

# What matters when caring for CE patients?

Let us look into the "conditions" and "environments"

## Patient perspective

A patient seeks help in the health services?

## Health staff perspective

Which problem / disease does this patient have?

The patient wants to get healthy

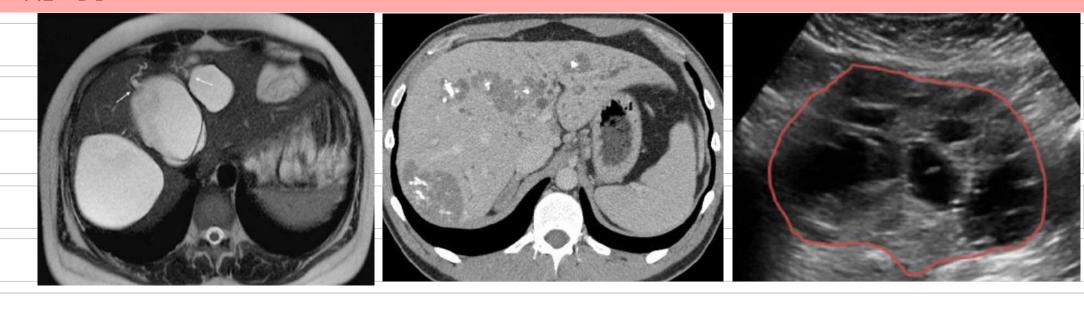
Health staff wants to diagnose and treat correctly

# Patient perspective Health staff perspective A patient seeks help in the health services? Which problem / disease does this patient have? Parasite – patient interaction Health system's response Patient's response

The patient wants to get healthy

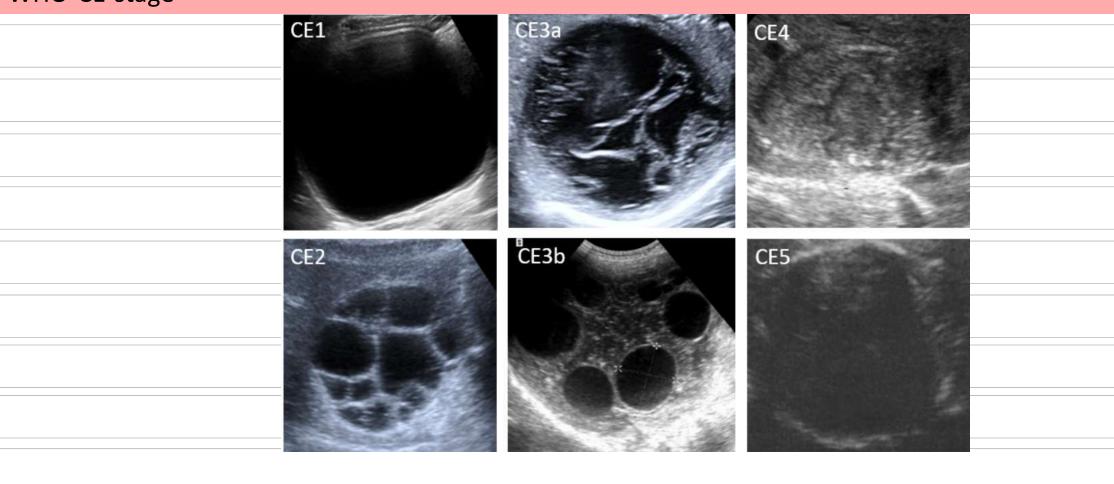
Health staff wants to diagnose and treat correctly

# CE – AE - DD



CE – AE - DD

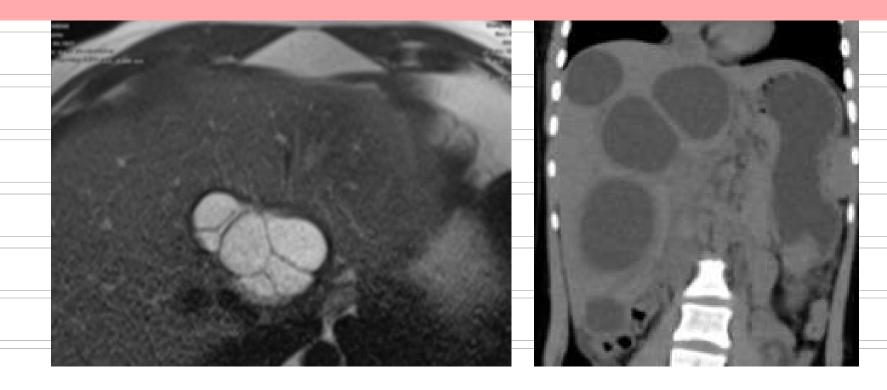
# WHO-CE-stage



CE – AE - DD

# WHO-CE-stage

# Size, number

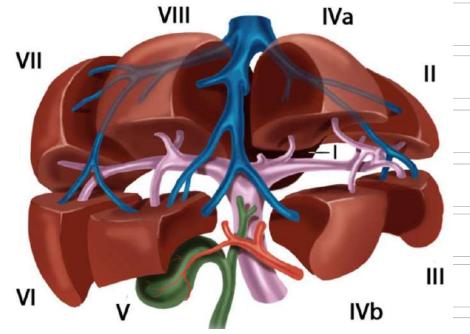


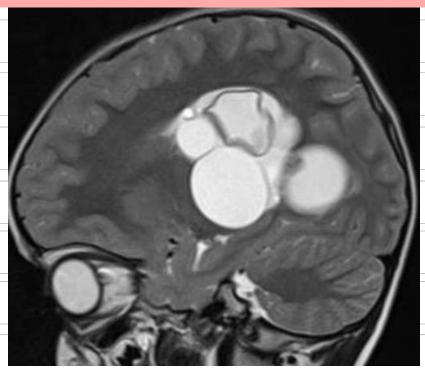
CE - AE - DD

WHO-CE-stage

Size, number

## Anatomical site





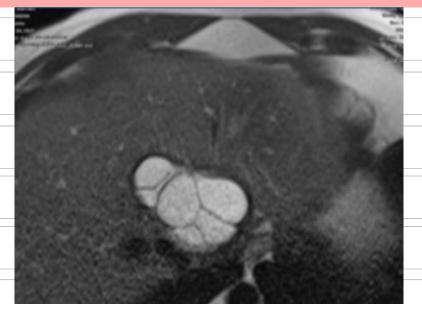
CE – AE - DD

WHO-CE-stage

Size, number

Anatomical site

# Uncomplicated - complicated





CE – AE - DD

WHO-CE-stage

Size, number

Anatomical site

Uncomplicated - complicated

# Health care setting





# **Infrastructure** stratified by health care level

	Low resource setting			High res	High resource setting	
	primary	secondary	tertiary	primary	secondary	tertiary
Infrastructure						
Emergency medicine	((x))	(x)	x	(x)	x	*
Surgery	8	(x)	x	27	x	×
Anaesthesia		(x)	x	£3	x	x
Hygiene	((-))	(x)	×	×	x	x

Echinococcosis
CE – AE - DD
WHO-CE-stage
Size, number
Anatomical site
Uncomplicated - complicated
Health care setting
Skills / experience

# **Skills** stratified by health care level

	Low resource setting			High resource setting		
	primary	secondary	tertiary	primary	secondary	tertiary
Skills						
Imaging (US)	S	(x)	×	×	×	×
Imaging (CT)	-	50	(x)	e.	x	×
Imaging (MRI)	20	Zi.	((x))	2	×	×
Laboratory (specific)	((x)) POC	(x)	x	(x)	x	×
Percutaneous methods	(E)	(x)	x	ž.	x	×
Surgery	왕	(x)	x	4	×	x
Anaesthesia	*	(x)	x		×	x

Echinococcosis
CE – AE - DD
CL - AL - DD
WHO-CE-stage
Ciza numbar
Size, number
Anatomical site
Uncomplicated - complicated
Health care setting
Skills / experience
materials
Thaterials

# **Resources** stratified by health care level

	Low resource setting			High res	High resource setting		
	primary	secondary	tertiary	primary	secondary	tertiary	
Resources							
US	-	(x)	X	. <b>x</b>	( <b>x</b> )	X	
СТ			(x)		x	×	
MRI	-		((x))		×	×	
Percutaneous methods	1.5	(x)	×	125	x	х	
Endoscopy	E	2	31	172	-	x	
Laboratory (specific)	((x)) POC	(x)	x	(x)	x	×	

Echinococcosis
CE AE DD
CE – AE - DD
WHO-CE-stage
Size, number
Anatomical site
Uncomplicated - complicated
Health care setting
Skills / experience
materials
Patient's economic situation

Echinococcosis
CE – AE - DD
WHO-CE-stage
Size, number
Anatomical site
Uncomplicated - complicated
Health care setting
Skills / experience
materials
Patient's economic situation
Patient's medical history

CE – AE - DD

WHO-CE-stage

Size, number

Anatomical site

Uncomplicated - complicated

Health care setting

Skills / experience

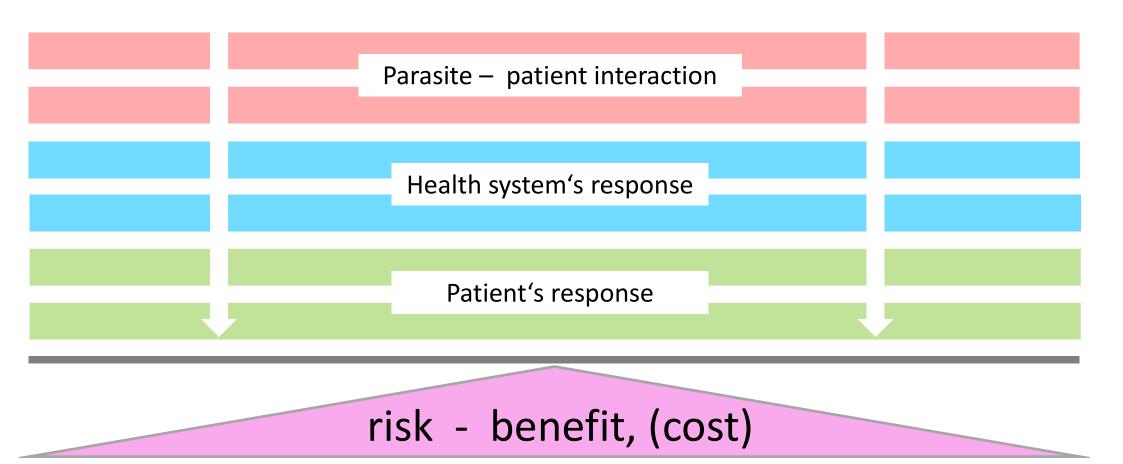
materials

Patient's economic situation

Patient's medical history

## Patient's preferences

# Going from evidence to recommendations



#### The WHO-IGWE 'CE Technical Manual'

#### A. Definitions

- B. Strategies
  - B.1. Diagnostic strategies
  - B.2. Clinical strategies
  - B.3. Health services strategies
- C. Tools to diagnose and stage CE
  - C.1. Imaging
  - C.2. Laboratory diagnosis
- D. Health services settings (level of infrastructure, resources, skills)
- E. Diagnosis, treatment and follow-up of **uncomplicated** cystic echinococcosis stratified by organs and treatment modalities (drug Rx, percutaneous Rx, surgery, watc & wait)
- F. Diagnosis, treatment and follow-up of **complicated** echinococcal cysts

- **G.** ANNEX: Evidence-base of diagnostic and treatment procedures
  - **G.1.** Imaging
  - **G.1.1.** Data extraction from published literature
  - G.1.2. Expert opinion, consensus and research needs
  - **G.2.** Laboratory

etc.

**G.3.** Antiparasitic-drug treatment

etc.

H. ANNEX: Research needs

I. ANNEX: Checklists

J. ANNEX: Training

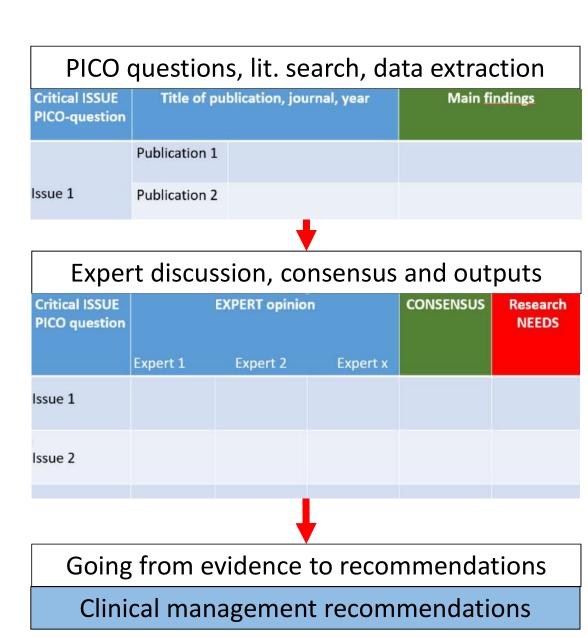
K. ANNEX: Useful links

L. ANNEX: References

## **CE Technical Manual**

ANNEX G

Chapters A to F





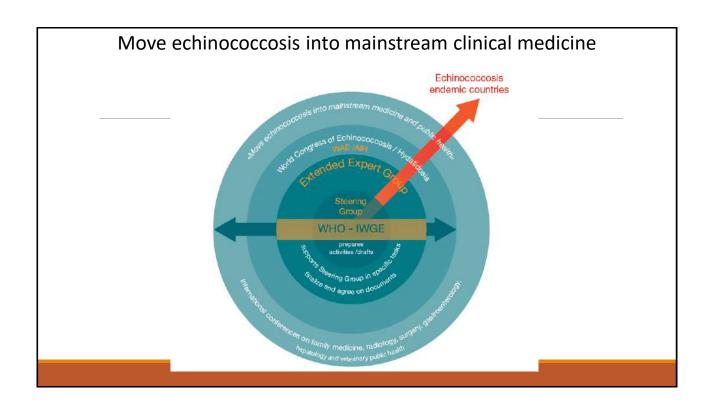
Imperial Palace Mosaic Museum (image public domain)





# Update from WHO-IWGE - AE Clinical group Building the AE Technical Manual

Laurence Millon,
On the behalf of the AE clinical group steering committee
(L Millon, B Gruener, B Muellhaupt, S Bresson-Hadni)



## Objective

To provide very concrete guidance on practical procedures and other patient management relevant features

With short text + algorithms, graphical work, photos, videos ...

"The 'AE Technical Manual' should NOT be a "textbook"

The user of the 'AE Technical Manual' wants to know,

- what is based on which grade of evidence extracted from published studies?
- what is based on personal experience of experts / AE treatment centres?
- what is not known at all and awaits clarification by future studies (research needs)?

## IWGE meeting in Geneva December 2016

# First organization of the steering group and working subgroups

- Imaging
- Laboratory diagnosis
- Medical treatment
- Surgery
- Endoscopy
- Data platform
- · Research gaps

#### IWGE AE subgre

- AE Clinical. Coordinators: L. Million (Besançon, France) and B. Mühfhaupt (Zurich, Switzerlane)
- Imaging.
  Coordinator: T Graster (Villa Germany), E Delabriousse (Berlangon, France)
  O Biogopidenov (Bezancon, France), Liu Wenya (Urumol, China), Bao Halivia (China),
  T Graster (Ulm Germany), E Delabrousse (Bezancon, France)
- Laboratory diagnosis.
   Coordinators: I Millor (Besançon, France).
   I Am (Urumqi, China).
   Gottstein (Ben, Switzerland).
   Therth. (Uru. Germany).
   J Minopo (Besançon, France).
   Grenoullet (Besançon, France).
   L Minopo (Besançon, France).
   L Minopo (Besançon, France).
- Medical treatment, developing Communi, C. Richeu (Besançon, France). Cardioletter, B. Grüser (Mo., Germany), C. Richeu (Besançon, France). Clinicolati. M. Stalkovi, Helecolatir, G. Brisson, Hennin, B. Bandon, France). De
- Surgery,
  Coordinators: IAN Halaing (Mining, Ohine), A Hillesbrood (Ulm Germany).
  D Henne Bunn (Ulm Germany): B Hane (Besungen, France), Wen Hee (Unmel Chine),
  SHOD Yognet, Desthabilisher Lursan (Muning, Chine), G select (Sussanse, Sentercised) N
  Halaik (Lausanne, Sultrelland). G Select (Sen., Selfterland), A Hillesbrood (Ulm Germany),
  Fen Halving (Mining, Chine)
- Coordinators: 5 Kach (Sesangon, France), M Sulz (St Gallen, Switzerland)
  Fan Haining (Kining, Chigha), Zhang Zhiqiang (Vrumqi, China), 5 Koch (Besançon France),
  Sulz (St Gallen, Switzerland)
- Data platform
   Coordinators: J Schmidberger (Ulm desmany), # Demonster (Besancon, France)
   Millon (Besancon France, J Knapp (Besancon, France), Li Bohn (Lituma), Xinjiang), SUN Lift
   (Liruma), Xinjiang), J J Sommidberger (Ulm Garmany), \* Domonment (Besancon, France)
- Research gaps.
   Coordinators: B Gottstein (Bern, Switzerland), LIM Renyong (Unump), Chico)
   AP Selanger (Besancon, France), L Million (Besancon, France) UN Renyong (Unump), Chica B Gottstein (Bern Switzerland)

## Since then,

2017-2018: several e-mails - ....

#### 2019:

- Involvement of more people in the steering committee
- Several e-mails + phone calls
- Work meetings

(Besançon, October 15; Lima October 30)

- → Proposal for a new organization of the sub groups (simpler/more operational)
- → Proposal for the structure of the AE technical manual content

## IWGE AE technical manual: working groups

Coordination of WHO-IWGE AE clinical group — L Millon, B Gruener, B. Mühlhaupt, S Bresson-Hadni

→ 4 IWGE-AE clinical subgroups

#### 1/ Diagnosis and follow up

- Imaging
- Lab tools

#### 2/ Treatment

- Medical/ Pharmacology
- Surgical
- Interventional

#### 3/ Data platforms

4/ Research

#### 1/ Diagnosis and follow up

Imaging

Rapporteur: T Graeter (Ulm Germany), E Delabrousse (Besançon, France)

Members: O Blagosklonov (Besancon, France), Liu Wenya (Urumqi, China), Bao Haihua (Xining, China),

Other members: ?

Lab tools

Rapporteurs: L Millon (Besançon, France), Li Jun (Urumqi, China), B Gottstein (Bern, Switzerland), Members: T Barth (Ulm Germany), A. Weber (Zurich, Switzerland), J Knapp (Besançon, France), H Auer (Austria), P Deplazes (Zurich, Switzerland)

Other members?

#### 2/ Treatment

Medical/Pharmacology

Rapporteur: B Gruener (Ulm, Germany), S Bresson Hadni ((Besançon, France) Members:

Clinicians: M Stojkovic (Heidelberg, Germany), C Richou (Besançon, France)

F Chappuis (Geneve, Switzerland), G Beldi (Bern, Switzerland), F Tissot (Lausanne, Switzerland), M Sulima (Poland), A Marcinkute (Lithuania), M Ramharter (Hamburg, Germany)

Pharmacologists: Wang Jianhua (Urumqi, China); D Montange (Besançon, France)

Surgical

Rapporteur: FAN Haining (Xining, China), A Hillenbrand (Ulm Germany)

Members: D Henne-Bruns (Ulm Germany), B Heyd (Besançon, France), C Turco (Besançon, France), ,
Wen Hao (Urumqi, China), SHAO Yingmei, Tuerhonhjiang Tursun (Urumqi, China), G Joliat (Lausanne,
Switzerland), N Halkic (Lausanne, Switzerland), G Beldi (Bern, Switzerland), A Lachenmayer (Bern,
Switzerland), C Toso (Geneve, Switzerland), O Detry (Liege, Belgique)

Interventional

Rapporteur: S Koch (Besançon, France), M Sulz (St Gallen, Switzerland)
Members: Fan Haining (Xining, Qinghai), Zhang Zhiqiang (Urumqi, China),

Other members?

#### 3/ Data platform

Rapporteur: J Schmidberger (Ulm Germany), F Demonmerot (Besançon, France)

*Members*: L Millon (Besançon France, J Knapp (Besançon, France), LI Bolin(Urumqi, Xinjiang), SUN Lin

(Urumqi, Xinjiang), Other members?

#### 4/ Research gaps

Rapporteur: B Gottstein (Bern, Switzerland), LIN Renyong (Urumqi, China) Members: AP Bellanger (Besançon, France), L Millon (Besançon, France),

Other members?

# IWGE AE technical manual: Methodology

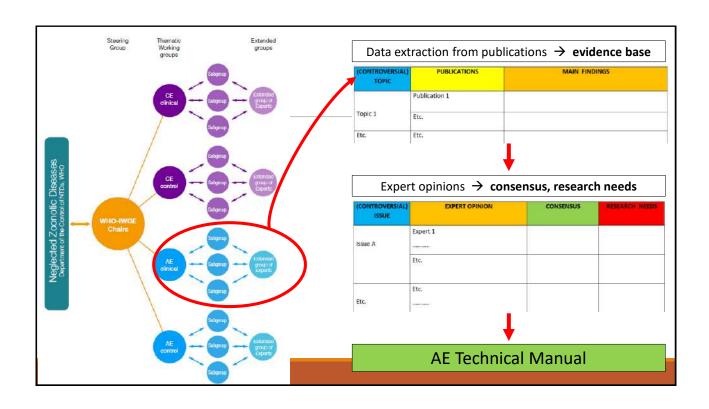
Methodology for writing the AE technical manual Similar as CE technical manual

Litterature + consensus of expert opinions

Consensual topics : Main draft proposed for reviewing

Controversial topics: opinions collected using similar form as for building CE

technical manual



## IWGE AE technical manual: Content

#### 1/ Diagnosis

- Immunocompetent/ Immunosupressed
- Minimum data (history, imaging, serology, molecular biology)
- Imaging US, CEUS, CT, MRI, PET CT, PET MRI,
- Case definition and staging

Minimal requirement for all countries
Specificities according to country ressources (optimum vs minimal)

#### 2/ Treatment

- BZM for all patients ?
- Immunocompetent/ Immunosupressed (steroids, chemotherapy, biological agent, rituximab, tacrolimus, HIV ... )
- Medical,
  - Pre BZM evaluation (comedication, diet habit ...)
  - Treatment before/after surgery, duration , stop criteria
  - · BZM plasma level/ pharmacological follow-up
- Surgery
  - Safety margin
  - Treatment before/after
  - Minimal invasive surgery
  - Ex vivo extensive surgery
  - Liver transplantation
- Interventional
  - · endoscopic/ radiologic
- New treatment strategy : radiofrequence ?
- Others

Minimal requirement for all countries Specificities according to country ressources (optimum vs minimal)

#### 3/ Therapeutic monitoring

- Definition cured /stable / progressive
- Operated/non operated
- · Frequency of monitoring
  - Imaging,
  - Serology Em2/ Em18
  - BZM plasma level /pharmacological follow-up
- Early detection of progressive disease / Non response

Minimal requirement for all countries
Specificities according to country ressources (optimum vs minimal)

Special topic for immunosuppressed patients

#### 4/ Pending questions

- Pregnancy
- Small incidental lesion
- How to handle BZM tocixity
- Role of UDCA in cholestatic AE patients
- Follow up after BZM interuption
- Radiofrequence and microwawe

#### 5/ Epidemiology/ Control

- Registry/ data platform
- Ecoepidemiology/ transmission/ prevention
- Need for screening

At risk population (farmer) Familial screening

#### 6/ Research gap

- Therapy
  - ABZ resistance ?
  - New drugs
  - New strategy / immunotherapy
- Monitoring /
  - New biomarker /viability
  - Imaging
- Other ...

## Conclusion

Still a lot of work ...

Call for people who want to join

Please send an e-mail to the coordinators

<u>Imillon@chu-besancon.fr</u>, <u>Beate.Gruener@uniklinik-ulm.de</u> <u>beat.muellhaupt@usz.ch</u>, <u>dr.bresson.hadni@wanadoo.fr</u> Vigilancia y control de Equinococosis quística

Dr. Edmundo Larrieu
Universidad Nacional de Rio Negro-La Pampa
Vicepresidente para América
Asociación Internacional Hidatidologia



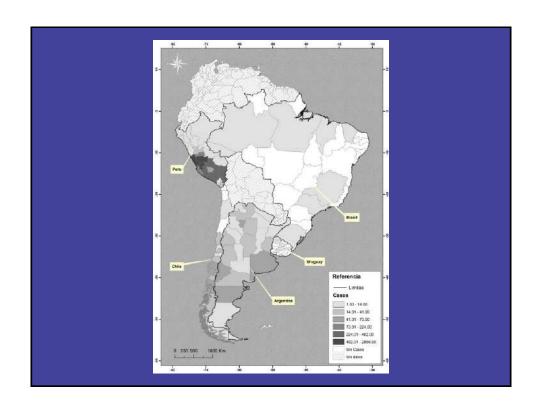


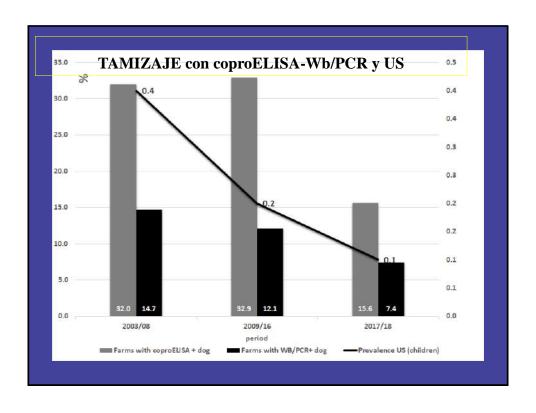
ACTION	Highlight for CE surveillance
Surveillance in	CoproELISA in dog and ELISA in lambs can give cross-reactions
farms	with other tapeworms. By the presence of dogs fed with raw viscera and / or insufficient deworming with PZQ. If the number of faecal samples or blood samples of the farm is representative of each one, the classification of a farm as positive will be adequate and useful for the surveillance in a control program, to determine farms where control measures should be increased, least until it is entered into the elimination phase that requires adjusting the specificity of the techniques used (for example PCR or lamb necropsy)
Surveillance in children	US screening is sensitive and specific to assess transmission in the recent past and to measure the evolution of prevalence with the control measures implemented.  The active search of cases through the US, in addition, allows to give timely treatments to the detected cases, reducing the complications of the disease, mortality and the costs of hospitalization.



- The South American Initiative for the surveillance, control and prevention of Cystic Echinococosis/Hidatidosis
   (Cases, Slaughterhouse, Us, coproELISA/PCR)
- Heracles in Bulgaria, Romania, and Turkey (US)
- PERITAS. Molecular-Epidemiological Studies on Pathways of Transmission and Long Lasting Capacity Building to Prevent Cystic Echinococcosis Infection (Us, coproELISA, ambient)

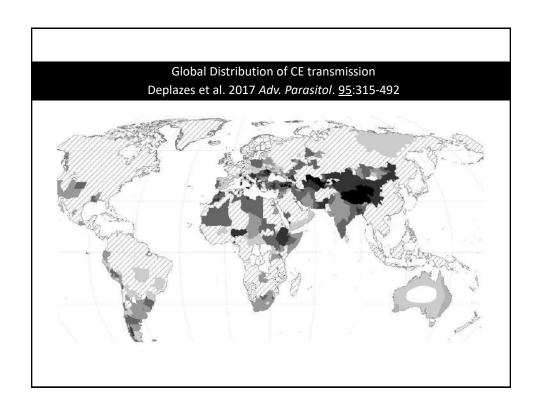
- Turkana (Us, surgical cases)
- Kyrgyzstan (coproELISA)
- China (Xiji County, coproPCR), (Ningxia Hui, coproPCR, ELISA) (Golog Tibetan, US, ELISA)





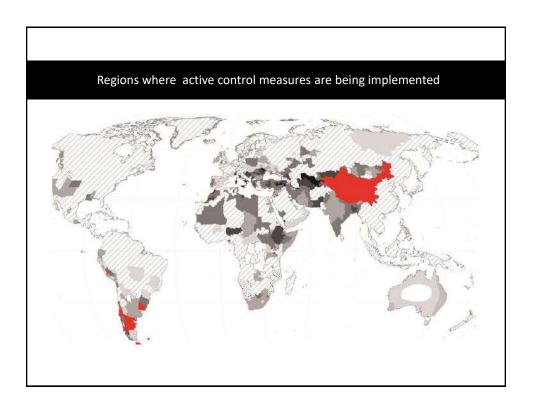


#### IWGE subgroup Control of CE



Survey of current active measures to control transmission of CE

- 68 people
- 25 countries



Country	Longstanding (>decade)	'New' initiatives	National	Regional	Pilot/ Project
Argentina	X			X	
Chile		Χ		Χ	
China	х		X		
Kyrgyzstan		Χ	Х		
Morocco		Χ			Х
Peru		Х			Х
Uruguay	Х		Х		

Limitations created by regulatory restrictions on who can undertake control activities in animals

- Morocco
- Kyrgyzstan

What human CE incidence level could differentiate:

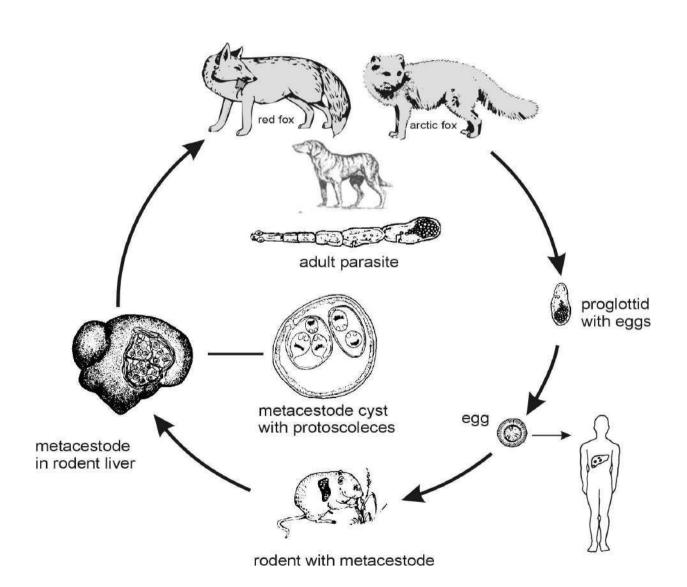
Countries/regions where CE is a public health problem vs
Countries regions regarded as "highly endemic"?

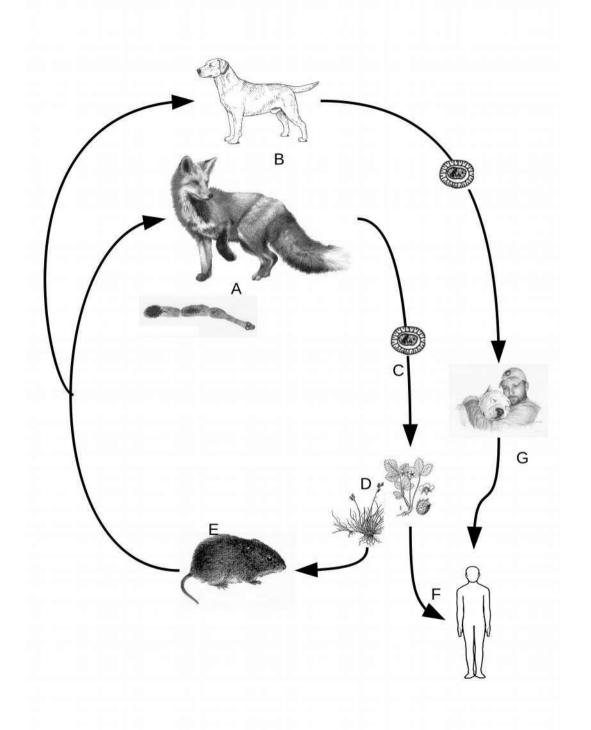
20/100,000?



# AE Control, an update Paul Torgerson

# Echinococcus multilocularis Universität Zürich





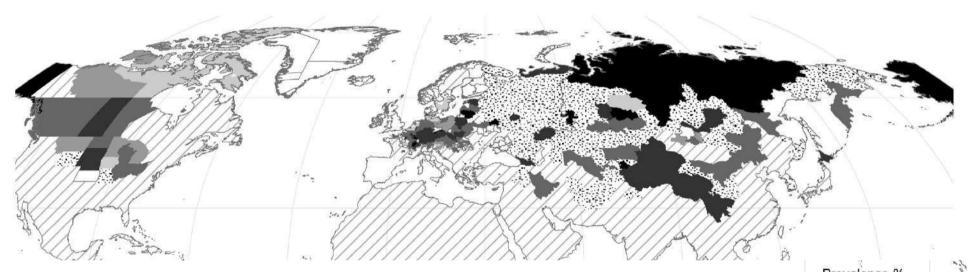




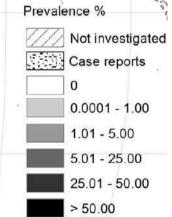
#### Veterinary Σpidemiology



#### **Alveolar Echinococcosis**



Prevalence in foxes

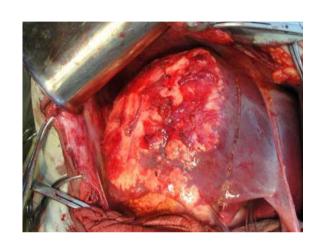


# Echinococcus multilocularis









High human incidence – China, central Asia
 High prevalence in dogs and foxes
 Asian genotype
Low human incidence – Europe
 High prevalence in foxes, low prevalence in dogs
 European genotype
Zero human incidence – Nth America\*
 High prevalence in foxes
 Nth American genotype

\*recently a few human cases have been detected due to possibly introduced European genotype



# Kyrgyzstan Prevalence - Foxes



151 foxes

Intestinal helminths	Numbers positive (prevalence %)	
Mesocestoides spp.	99(65.6)	
Dipylidium caninum	50(33.1)	
Taenia spp.	48 (31.7)	
Echinococcus multilocularis	96(63.6)	
Toxocara canis	46 (30.4)	
Toxascaris leonina	9(5.9)	
Capillaria spp.a	34(22.5)	
Acanthocephala spp.	2(1.3)	



# Kyrgyzstan - Dogs

### 466 dogs

Parasite	Prevalence
E. granulosus	19%
E. multilocularis  Dogs allowed to roam  Dogs not allowed to  roam	18% 26% 11%





## Kyrgyzstan – Human AE

# Intense Focus of Alveolar Echinococcosis, South Kyrgyzstan

Human alveolar echinococcosis (AE) is a highly pathogenic zoonotic parasitic disease caused by *Echinococcus multi-locularis*. An ultrasound study in southern Kyrgyzstan during 2012 revealed a prevalence of 4.2% probable or confirmed AE and an additional 2.2% possible AE, representing an emerging situation. The risk for probable or confirmed AE was significantly higher in dog owners.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 6, June 2018

# Transmission, AE Kyrgystan



Natural cycle Foxes - prevalence 64%





Domestic Transmission Dogs prevalence 19%

Zoonotic Transmission 6.7 cases/100,000



# Control of Alveolar Echinococcosis hygiene: wash / cook food deworm dogs wash hands avoid contact to foxes control foxes hunting limit food resources deworm foxes control interprevent dogs from mediate hosts predation on rodents



# Fox Elimination

Not practical

Very high reproductive rate of foxes

Just lowers the age of the fox population

Ecologically unacceptable?

*But....* 

Reuben island Japan

Small island – 83km<sup>2</sup>

Foxes and AE introduced c 1925

Foxes successfully eliminated by 1950s

111 cases of AE diagnosed before 1964

No new cases after 1994.



# Fox Treatment

Periodic anthelmintic treatment

Distribution of baits impregnated with

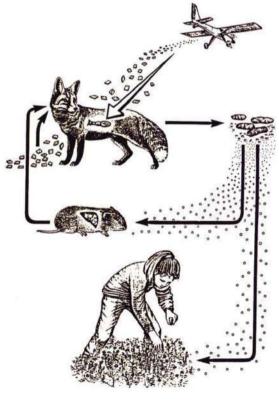
praziquantel

**Switzerland** 

Germany

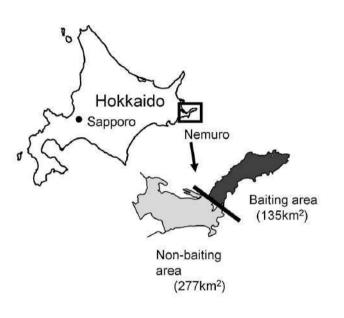
Japan







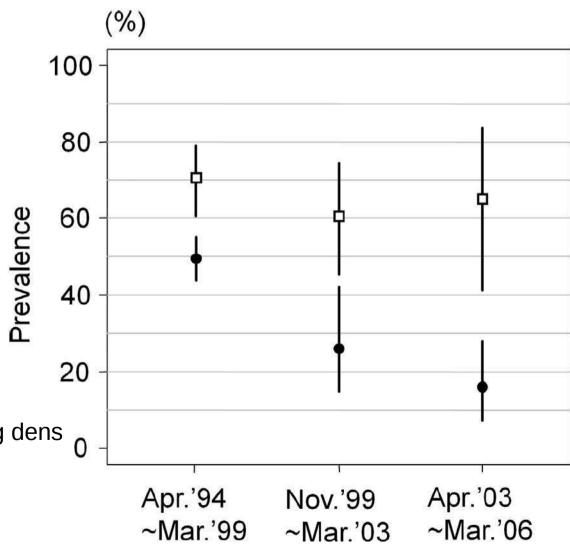
# Hokkaido Japan



Baits distributed at 15/km2

Average of 4.3 times per year

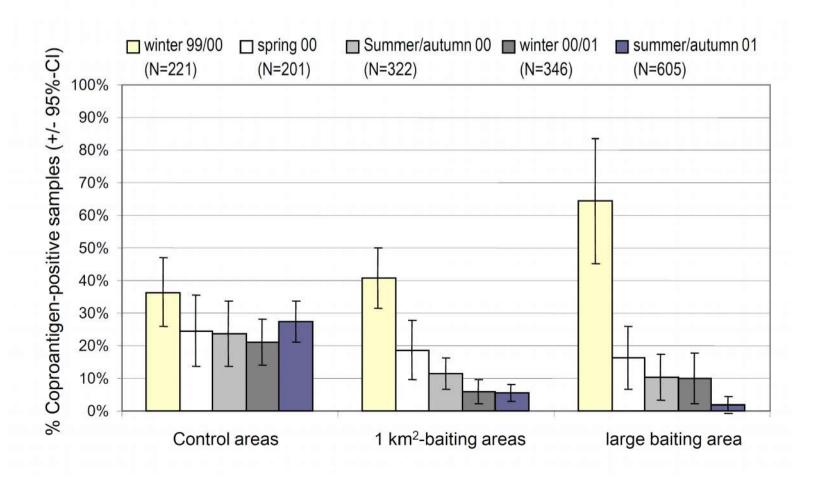
Additional baits round fox breeding dens





# Zürich Switzerland

Faeces positive for *E. multilocularis* coproantigen in baited and in control areas (N=1205)



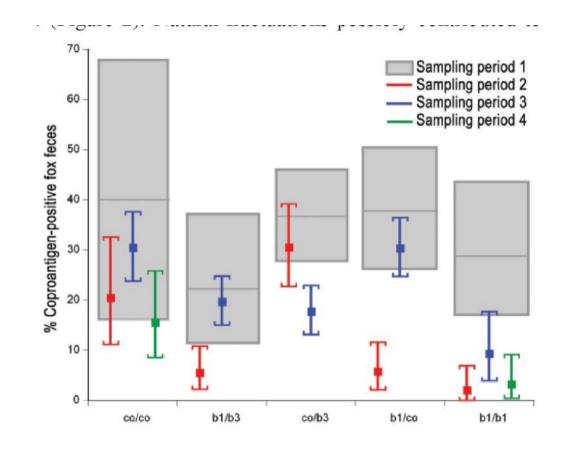


# Zürich Switzerland

# Control Strategy for *Echinococcus* multilocularis

#### **Daniel Hegglin and Peter Deplazes**

Echinococcus multilocularis, the causative agent of zoonotic alveolar echinococcosis, can be controlled effectively by the experimental delivery of anthelminthic baits for urban foxes. Monthly baiting over a 45-month period was effective for long-lasting control. Trimonthly baiting intervals were far less effective and did not prevent parasite recovery.





## Germany, 50 baits / km<sup>2</sup>

# Change of prevalence over time in the deworming and control area (confidence interval 95% both sides, N = 1575).

Table 1. Change of prevalence over time in the deworming and control area (confidence interval 95% both sides [31], N = 1575).

		Baiting area			Control area				
Period	Baiting intervall	no. examined / positive	% positive	CI—95%	CI + 95%	no. examined / positive	% positive	CI—95%	CI + 95%
2002/2003	No baiting	112/ 58	51.8	41.6	61.8	164 / 85	51.8	43.9	59.5
2005	No baiting Jan—Nov	56 / 21	37.5	24.3	51.0	41 / 16	39.0	24.0	55.5
2006	4 week	160 / 8	5.0	2.0	10.0	77 / 27	35.1	25.1	46.1
2007	6 week	169 / 4	2.4	0.9	5.4	50 / 11	22.0	11.5	36.0
2008	6 week	125 / 3	2.4	0.7	5.9	34 / 12	35.3	19.8	52.3
2009	6 week	152 / 4	2.6	0.1	6.6	63 / 15	23.8	13.8	35.8
2010	10 week	165 / 2	1.2	0.0	3.5	51 / 10	19.6	9.6	33,4
2011	10 week	88 / 0	0	0.0	4.0	22 / 6	27.3	10.3	45.8
2012	No baiting	28 / 3	10.7	3.8	26.8	15 / 6	40.0	28.5	64.0
Sum	Baiting period	859 / 21	2.4	1.6	3.4	297 / 81	27.3	21.3	33.8

König A, Romig T, Holzhofer E (2019) Effective long-term control of Echinococcus multilocularis in a mixed rural-urban area in southern Germany. PLOS ONE 14(4): e0214993. https://doi.org/10.1371/journal.pone.0214993 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0214993





#### Fox elimination

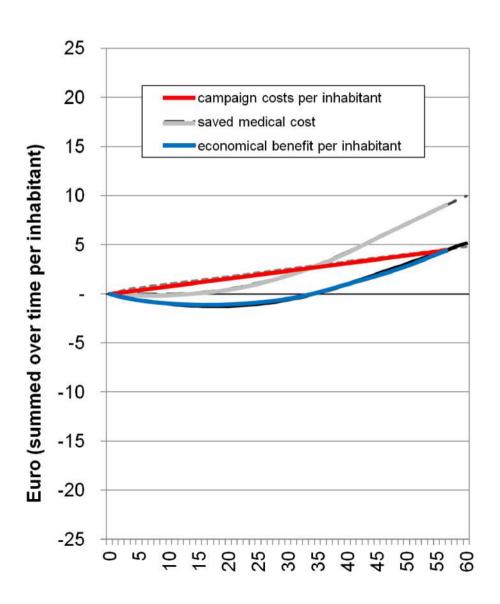
- One small island
- Effective in eliminating *E. multilocularis*
- Logistically and ecologically not possible on a larger scale

### **Baiting foxes**

- Reduces prevalence in foxes over limited areas
- Logistically challenging over a larger area
- Unclear yet of effects in human incidence
- Cost benefits?

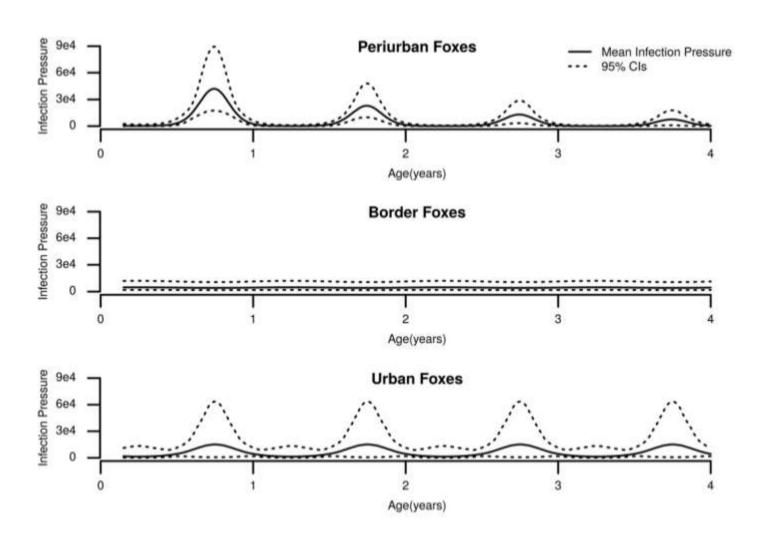


# Fox baiting – cost benefit?





# Fox baiting – cost benefit?



Foxes heavily infected late winter and early spring, lightly infected in summer and autumn Target treatments at this time to reduce costs?



Where dogs are infected and believed to be an important source of human infection

Often co endemic areas with *E. granulosus* 

China, Kyrgyzstan

Periodic anthelmintic treatment will control both parasites

Increased treatment frequency for *E. multilocularis*Shorter pre patent period

St Lawrence island, Alaska

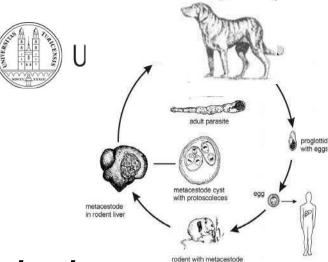
Highly endemic for *E. multilocularis* 

Monthly treatment of dogs

Reduce prevalence in voles from 29% to 5% over 2 years

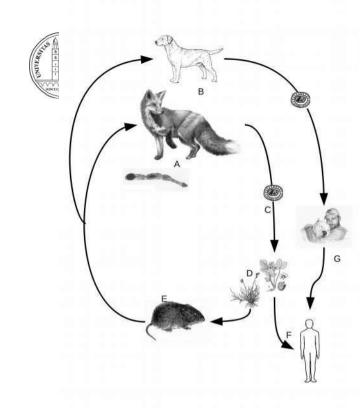
Dogs participate in cycle

Transmission to humans ceased



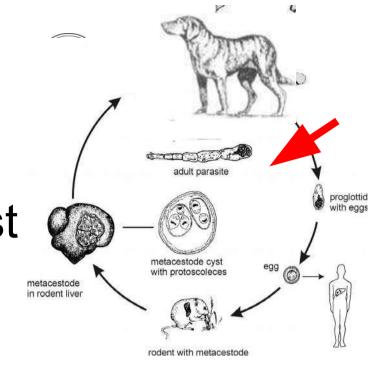
Shiqu County, China
Monthly dog treatment
2004 prevalence dogs – 7.2%
2016 0.55%
Human prevalence decreased

6.2% to 3.7%



No change in prevalence in small mammals

Dogs are main definitive host
St Lawence Island
Treating dogs breaks cycle
Elimination may be possible

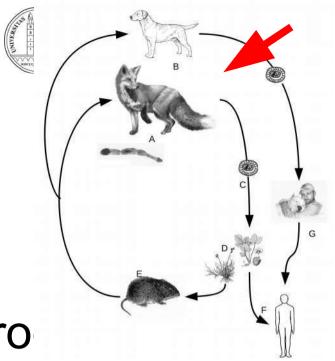


Shiqu, China

Dogs spill over definitive host

Treating dogs has no effect fox-rocycle

Treating dogs indefinitely to reduce transmission to humans







Source attribution

Fox contact?

Dog contact?

Contaminated food (eg berries)?

Water

Other



# Dog contact

Study	Attributable Fraction	
Wang et al 2006a	0.634	
Wang et al 2006b	0.594	
Yang et al. 2006	0.095	-
Schantz et al. 2003	0.393	- <del></del>
Craig et al. 2000	-0.191	<u> </u>
Wang et al. 2001	0.565	
Wang et al. 2004	0.634	
Han et al. 2009	0.449	
Dawei et al. 2015	0.265	
Babesov et al. 2018	0.497	
Summary Cross Sectional Studies	0.357	•
Shi et al. 2004	0.375	
Kern et al. 2004	0.352	
Kreidl et al. 1998	-0.039	
Piarroux et al. 2013	0.488	— <b>—</b>
Stehr-Green et al. 1988	0.643	
Summary Case Control Studies	0.331	•
Summary All Studies	0.344	
	-1	Attributable Fraction (+/- 95% CI)

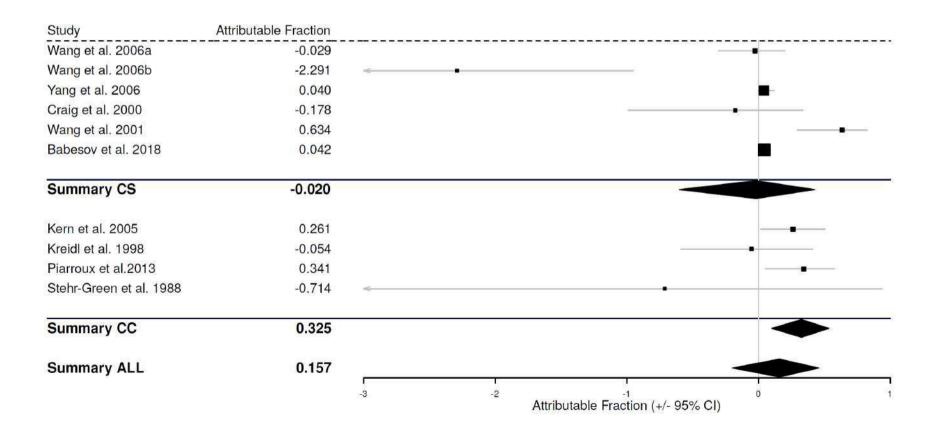


### **Contaminated Water**

Study	Attributable Fraction	
Wang et al. 2006a	0.088	<del></del>
Wang et al. 2006b	0.483	-
Yang et al. 2006	0.187	-
Wang et al. 2001	0.424	
Wang et al. 2004	0.310	-
Babesov et al. 2018	0.113	-
<b>Summary Cross Sectional Studies</b>	0.276	
Kern et al. 2004	0.097	
Summary All Studies	0.248	
	-1	0 1
		Attributable Fraction (+/- 95% CI)



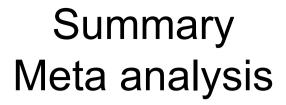
### **Contaminated Food**





### **Fox Contact**

Study	Attributable Fraction	
Wang et al. 2006a	1.000	
Wang et al. 2006b	1.000	<
Craig et al. 2000	0.002	-
Wang et al. 2001	-0.124	
Babesov et al. 2018	0.005	•
Summary Cross Sectional Studies	-0.011	
Kern et al. 2004	-0.009	+
Piarroux et al. 2013	0.188	
Stehr-Green et al. 1988	-0.085	
Summary Case Control Studies	0.230	
Summary All Studies	0.140	
		-2 -1 0
		Attributable Fraction (+/- 95% CI)





Strong evidence for dog – human transmission

Strong evidence for contaminated water Weak evidence for food borne AE

But may be important in low endemic areas

Weak evidence for fox- human contact











# Control – prevent introduction

Risk assessment of importation of dogs infected with *Echinococcus multilocularis* into the UK

P. R. Torgerson, P. S. Craig

Veterinary Record (2009) 165, 366-368

Without praziquantel treatment of dogs before entry into the UK introduction is almost inevitable

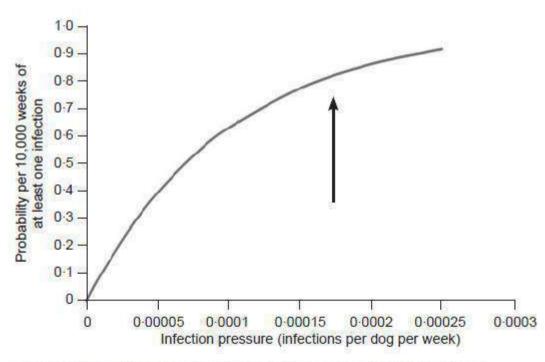
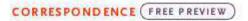


FIG 2: Probability of at least one infection per 10,000 weeks of exposure. The solid arrow represents the estimated infection pressure to dogs in Germany. Thus for every 10,000 dogs there is a probability of approximately 0.85 that at least one dog is exposed per week, rising to 0.98 over a two-week period



## Control – prevent introduction



### European Echinococcus multilocularis Identified in Patients in Canada

July 25, 2019

N Engl J Med 2019; 381:384-385 DOI: 10.1056/NEJMc1814975

Echinococcus multilocularis is widespread in Canada and USA North American Genotype
Only one confirmed case of human AE due to this genotype
Recently European genotype detected in wild caniids
Now human cases have appeared

Introduced with a dog from Europe??



## Conclusions

## Target dog to human transmission

- High endemic areas
- Periodic anthelmintic control
- Dog control
- Prevent access to rodent IH

#### Fox to human transmission

- Pilot studies in low endemic areas suggest it is possible
- May be cost effective over long term

Controls of dog movements into non endemic areas (if possible!!)

- Eg UK, Ireland
- Praiquantel treatment of all dogs before admittance.





## International consensus on terminology in the field of echinococcosis



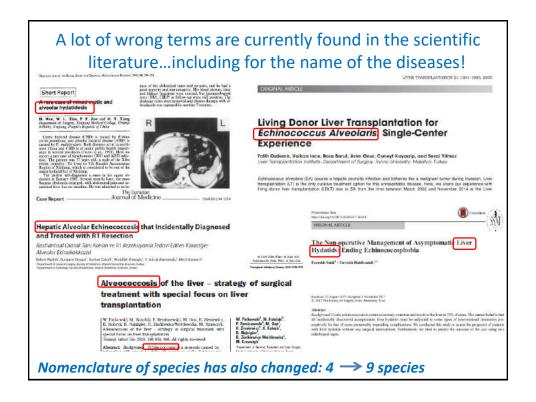
\*Vuitton Dominique A., Tuerhongjiang Tuxun, Rogan
Michael T, McManus Donald P, Menezes da Silva Antonio,
Naidich Ariel, Romig Thomas, Gottstein Bruno, Wen Hao,
for the World Association of Echinococcosis and the WHOInformal Working Group on Echinococcosis.

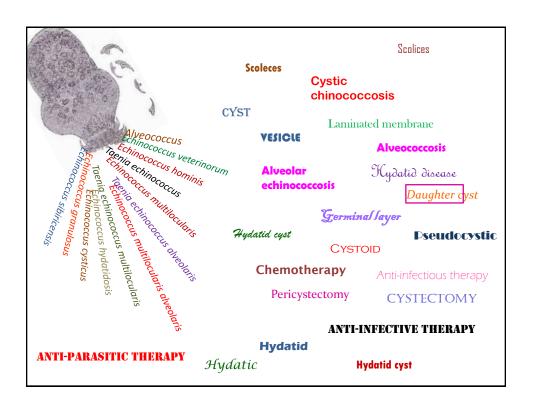
French National Reference for Echinococcoses ; Besançon University Hospital & University Bourgogne Franche-Comté, France

# History, geography and languages in the field of echinococcosis

- Words and expressions built from various languages, following the advancement of science and recognition of the disease in various endemic countries
- 'False-synonyms', different in the various endemic countries, because of the local language of the professionals, and wrong translation into English...







Why do we need to agree on common words/expressions in scientific communication/publication on echinococcosis?

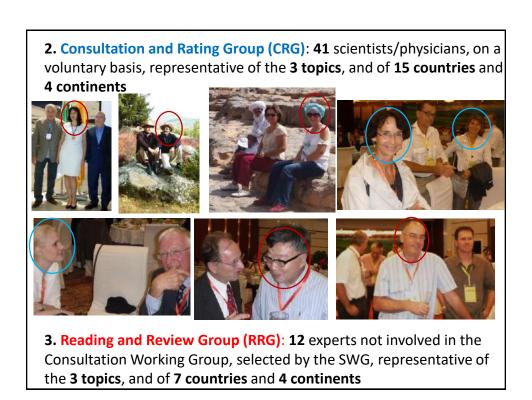
- Studies on Echinococcus spp. are multidisciplinary: the various disciplines sometimes use the same words with different meanings; this adds to create 'false-synonyms' and confusion
- These various disciplines within science and within medicine must cooperate to solve the multiple problems of *Echinococcus* spp. infection ('One-Health' concept). This makes the use of a common vocabulary crucial in the 21<sup>st</sup> century
- English is the worldwide accepted common
   Organisation mondiale de la santé

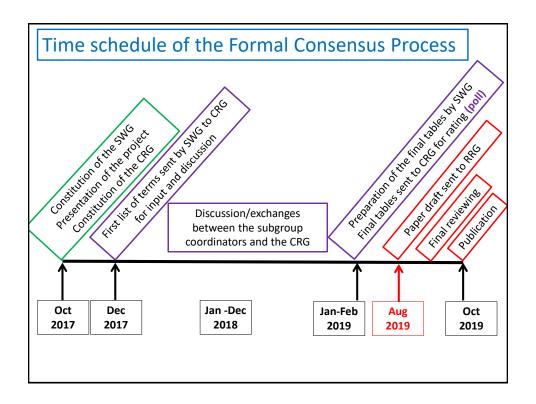
   scientific language: agreement should begin with who-Iwge
   English terms and expressions.

AIMS of the WAE and WHO-IWGE for the work on nomenclature/terminology

- To provide a basis for discussion and decision on the accepted words/expressions in English to designate the parasites of the Echinococcus genus, and related diseases
- To reach a consensus after further scientifically- and/or historically- and/or linguistically-based discussion with the recognized specialists of each field
- To publish this consensus in an internationally indexed journal with free access to papers







#### Formal consensus process

 1st step: Preliminary list of 'sensitive issues' regarding words and expression commonly used in the scientific/medical literature on echinococcosis, with arguments and references: comments and discussion within the SWG and CRG

Word/expression	Definition	Reasons for acceptance	Reasons for rejection		
Denomination of diseases					
Echinococcosis	All diseases related to	Recommended by the World Federation of			
(Plural:	infection with parasites	Parasitologists (WFP) (i.e. name of the genus –osis)			
Echinococcoses)	of the Echinococcus	The English name of the World Association of			
	genus	Echinococcosis was modified in 2015 to follow this rule			
Hydatidosis	Disease related to	Historical name for the infection due to E. granulosus	-not only Echinococcus spp develop		
	infection with E.	s.l.	'hydatids';		
	granulosus s.l.		-does not fit with the unified		
			recommendations of the WFP		
			-when used wrongly for E. mutilocularis		
			infection, increases the confusion of		
			clinicians between the diseases due to E		
			granulosus s.l. and E. multilocularis		
			respectively		

- 2<sup>nd</sup> step:
  - 3 lists of 'approved terms', 'rejected terms', for all 3 topics, and 'debated issues submitted to poll', for 'Biology & immunology' and 'Clinical aspects.
  - Independent rating of each 'debated' words and expressions (from 0 to 10): results according to the agreement of voters and median value.
- 3<sup>rd</sup> step: 2 lists of 91 approved and 58 rejected terms (Tables 1 & 2, ABC) + text &

Word/ Expression	Definition	Arguments for acceptance; references; linguistic precisions	Comments
Echinococcus oligarthra (Diesing, 1863)	A species in the genus Echinococcus	E. oligarthra (Diesing, 1863)[14] is a species found in South, Central and North America (Mexico)[53,59]. The component 'arthra', originally proposed by Diesing, comes from the ancient Greek ἄρθρα –arthra (joints) which is the plural of ἄρθρον –arthron (joint). The name is therefore not an adjective, but a noun in apposition, which does not change its ending according to the gender of the generic name. This was recognized earlier but subsequently ignored.	E. oligarthra cycle usually involves paca (Cuniculus paca Linnaeus 1766) as intermediate host and various wild cat species as definitive hosts[66]. It is responsible for a disease in humans distinct from cystic and alveolar echinococcosis, sometimes wrongly called 'polycystic echinococcosis' (since it usually presents as a single cyst)[36]. 'Neotropical echinococcosis' is the expression recommended to qualify human infection due either to E. vogeli or to E. oligarthra. See also Table 1C
E. ortleppi Lopez- Neyra and Soler Planas, 1943	A species within E. granulosus sensu lato	E. ortleppi Lopez-Neyra and Soler Planas, 1943 [52] corresponds to the previous 'G5' strains, identified by DNA sequencing [1,53,67] (see GenBank: https://www.ncbi.nlm.nih.gov/genbank/)	E. ortleppi cycle usually involves cattle as intermediate hosts and dogs as definitive hosts; other ungulates may also be infected by E. ortleppi. Human cases are known, but rare [13]

Word/ expression	Definition	Reasons for rejection References; linguistic precisions	Comments
*cystoid, Adjective  [adjective common to  'Biology and immunology' and to 'Clinical Aspects']	Irregular cyst-like anatomical entity (and image) due to the central necrosis in advanced AE lesions.	As this cavity does not correspond to a parasitological entity, a specific word should differentiate this pathological cyst-like macroscopic structure from the real 'cyst' of CE.  This alternative to 'pseudocystic', includes the suffix '-oid' i.e. child off which looks like something). Opposite to 'pseudocyst / pseudocystic', it does not exist as a noun, only as an adjective.	Alternative adjective to 'aborted',     'cystoid' seems to be more common in German and German-derived languages. Less accessible to researchers speaking non-European languages than 'pseudocyst', it may induce more confusion with 'cystic', the adjective for the real 'cyst' of CE. Rejected by the majority of voters in the 'Biology and immunology' subgroup of the CGR (median: 1).
*died-out (cyst, lesion) , Adjective	Non-viable parasitic structure as evidenced by imaging (complete calcification in AE, CE5 cyst in CE) or histological examination (absence of viable parasitic cells).	Could be used in clinical or experimental situations when evidence of absence of viability is not obtained by transplantation or in vitro culture.	Rejected by a narrow majority of voters in the 'Biology and immunology' subgroup of the CGR (6/10).

#### Examples of \*discussions and \*\*votes

#### Names of *Echinococcus* spp.-related diseases

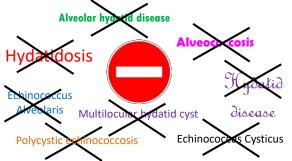
Only 3 names for 3 types of diseases

- \*Cystic echinococcosis (\*E. granulosus sensu lato)
- \*Alveolar echinococcosis (\*E. multilocularis)
- \*\*Neotropical echinococcosis (\*E. vogeli and \*E. oligarthra)



#### Names of *Echinococcus* spp.-related diseases

 All other names are rejected and should be abandonned!

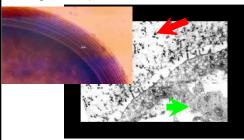


One use of 'hydatid' tolerated: as an adjective to designate only structures related to *E. granulosus sensu lato* (e.g. 'hydatid cyst', 'hydatid fluid')??? Still in debate...!

#### **Examples of \*discussions and \*\*votes**

The laminated layer should not be considered as a 'membrane' because:

• It is not a tissue. It is an extracellular secretion of the germinal layer tegument (which is not a membrane either!)



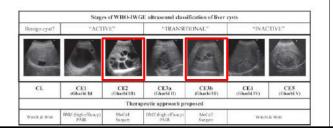
 This is also true for the 'adventitial layer' (multiple types of cells and matrix components)

It is thus preferable to use the term 'layer' for all 3 'layers' that constitute the **CE cyst** (recommended expression).

# Agreement between parasitologists and clinicians on the definition of the CE cyst

Description of the **\*\*CE cyst** (from inside to outside):

- √\*\*Cyst fluid (or \*\*hydatid fluid, for \*E. granulosus sensulato only)
- √\*Germinal layer (of the \*\*metacestode)
- √\*\*Laminated layer (of the metacestode)
- √\*\*Adventitial layer (of host's origin, but part of the 'cyst')



The difficult issue of the 'daughter cysts'...

# Consequences for surgery terminology The adventitial layer is part of the cyst is not 'pericystic' is not of parasitic origin "Pericyst" is the normal liver (or other organ) tissue around

...So, the operation which removes the adventitial layer is a TOTAL CYSTECTOMY and not a Pericystectomy!

The term 'pericystectomy' should be abandonned!

#### 1. Discussions on the 'medical' treatment of echinococcosis

- « chemotherapy »: used for cancer treatment, not for infectious diseases
- ➤ Vote on alternative words/expressions

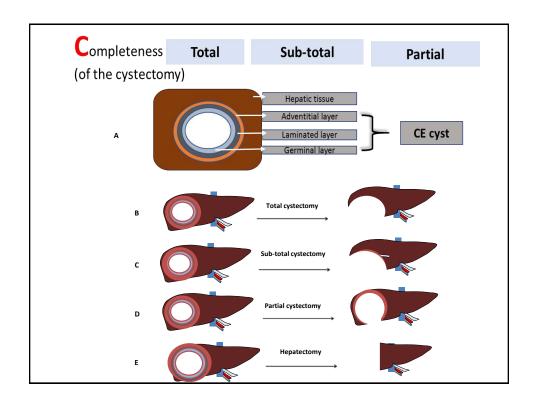
the 'cvst'

« anti-parasitic (drug) treatment »: unanimously accepted by voters (median: 10)

#### 2. Towards the 'AORC' system of description of CE surgery

- Aim: to describe surgical procedures used for Cystic Echinococcosis in a standardized manner
  - To provide a frame that may be used for more detailed description (surgery reports),
  - To enhance comparisons between published studies,
  - To base similar description in other languages than English (Chinese, French, Spanish, Portuguese, Arabic, Iranian, etc.).

Approach, Opening	, Resection and Completene	ss, AORC nomenclature sy	stem for CE surgery
$oldsymbol{A}$ pproach	Laparotomy	Laparoscopy	Robotic
Opening	Opened cyst OP	Non-opened cyst NO	Р
Resection	Cystectomy	Hepatectomy	Liver Transplantation
Completeness	Total cystectomy	Sub-total cystectomy	Partial cystectomy



#### And then...

- Submission of the Position Paper to the Journal 'Parasite'
- Publication of the Position Paper
- Similar work to be done for other languages: Chinese, Russian, Arabic, Spanish, Italian, French, Turkish, etc.



Towards a 'Multilingual Atlas of Echinococcosis'??