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THE FIRST MEETING OF THE WHO GUIDELINE DEVELOPMENT GROUP FOR THE REVISION OF THE WHO 1999 GUIDELINES FOR IODINE THYROID BLOCKING

Christoph Reiners[1,*], Rita Schneider[1], Makoshi Akashi[2], Eli A. Akl[3], Jean-René Jourdain[4], Chunsheng Li[5], Christoph Murith[6], Lodewijk Van Bladel[7], Shunichi Yamashita[8], Hajo Zeeb[9], Paolo Vitti[10] and Zhanat Carr[11]
[1]University Hospital Wuerzburg, Oberduerrbacher Str. 6, 97080 Wuerzburg, Germany
[2]National Institutes for Quantum and Radiological Science and Technology (QST), 4-9-1 Anagawa, Inage-ku, 263-8555 Chiba, Japan
[3]Department of Internal Medicine, American University of Beirut, Riad-El-Solh 1107 2020, P.O. Box: 11-0236, Beirut, Lebanon
[4]Institut de Radioprotection et de Sûreté Nucléaire, B.P. 17, 92262 Fontenay-aux- Roses, France
[5]Radiation Protection Bureau, Health Canada, 775 Brookfield Rd, Ottawa, Canada K1A 1C1
[6]Division Radioprotection de l'Office Federal de la Santé Publique, Schwarzenburgstrasse 157, CH-3003 Berne, Switzerland
[7]Federal Agency for Nuclear Control, Ravensteinstraat 36, B-1000 Brussels, Belgium
[8]Department of Radiation Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 8528523, Japan
[9]Leibniz-Institute for Prevention Research and Epidemiology (BIPS), Achterstraße 30, 28359 Bremen, Germany
[10]Endocrine Unit, Department of Clinical and Experimental Medicine, University Hospital, Via Paradisa, 2, 56124 Pisa, Italy
[11]Department of Public Health, Environmental and Social Determinants of Health, World Health Organization, 20 avenue Appia, 1211 Geneva-27, Switzerland

*Corresponding author: reiners_c@ukw.de

The meeting held in May 2014 in Würzburg, Germany, discussed the scope of the revision of the 1999 WHO guidelines for iodine thyroid blocking (ITB) by following the WHO handbook for guideline development. This article describes the process and methods of developing the revised, evidence-based WHO guidelines for ITB following nuclear and radiological accidents, the results of the kick-off meeting as well as further steps taken to complete the revision.

INTRODUCTION

Nuclear accidents or nuclear detonation scenarios include release into environment of radioactive iodine, such as I-131, among the other radioactive isotopes. The released I-131 will contaminate surfaces, soil, vegetation that can be consumed by people, as well as drinking water and milk produced by cattle consuming contaminated grass and/or water. Ingested and inhaled I-131 will be accumulated in the thyroid gland due to the specific metabolic pathway of iodine, where it will cause exposure of thyroid cells and the gland tissue to beta-radiation, leading to a risk of developing thyroid cancer. Young children are especially vulnerable to the exposure to I-131 and are at higher risk of developing thyroid cancer, as seen in the Chernobyl studies[1]. The exposure to I-131 can be prevented or significantly reduced, if the thyroid gland was saturated by stable iodine/iodide—an urgent protective action named iodine thyroid blocking (ITB)—thus preventing uptake and accumulation of I-131 in the thyroid[2]. This can be achieved by administering potassium iodide (KI) shortly before or immediately after the exposure. Pre-distribution of KI is a common practice around the nuclear power plant (NPP) operation, as a part of the emergency response planning[3, 4].

The WHO published 'Guidelines for Iodine Prophylaxis following nuclear accidents' in 1999[4]. In view of the upcoming revision, these guidelines were revisited and a systematic review of literature was conducted in 2010 on the current status of the evidence and adverse effects of KI[5]. A new WHO guideline development policy was introduced in 2009 as a formal protocol applying evidence-based approach, as described elsewhere[6].

In the light of the lessons learnt from the Fukushima Daiichi NPP accident, the issue of KI thyroid blocking came into light, as many countries reviewed and revised their national preparedness plans.

The European Commission (EC) has conducted a survey of the ITB policies in the EC countries and concluded that there is a range of differences in

policies between countries—in terms of planning, dosage and pharmaceutical form of KI, as well as distribution priorities among various affected population groups (babies, children, adolescents, adults, pregnant and breastfeeding women and those above age 40)[7].

To address the need for the updated WHO guidelines on ITB, a Guideline Development Group (GDG) was formed and a new title was recommended, which is called 'WHO Guidelines for ITB in a nuclear or radiological emergency', or ITB in short. This new title reflects the increase in scope to include radiological emergencies. The term 'iodine thyroid blocking' has been used as a substitute for 'iodine prophylaxis' in order to avoid confusion with prophylaxis of iodine deficiency disorders.

OBJECT

The 2014 meeting was a follow-up to three previous review meetings held in March 2008 at the WHO in Geneva, Switzerland, in July 2008 in Pisa, Italy and in January 2009 in Wuerzburg, Germany. These meetings discussed the state of knowledge, reviewed new evidence and scope of the revision. However, the revision process had to be put on hold after the Fukushima accident in 2011.

The object of the meeting convened on 10 May 2014, in Wuerzburg, Germany, was to revisit once again the revision of the 1999 WHO 'Guidelines for Iodine Prophylaxis following Nuclear Accidents' in line with the new WHO policy on guidelines development, and to review the updated evidence base taking into account additional data from recent studies on Chernobyl affected populations and new evidence generated after the Fukushima nuclear accident.

The guidelines are expected to assist Member States to develop national policies in line with international recommendations by the WHO, to meet the demand for harmonisation of the KI policy, and to establish the international benchmark on KI use policy.

This article describes the methodology of the guideline revision process, the results of the kick-off meeting and further steps to be taken.

METHODS

The WHO guideline development process

The development of these guidelines will follow the process described in the second edition of the WHO handbook for guideline development[6]. This process could be divided into planning, development and publishing phases. The planning phase includes forming a guideline steering group, determining the scope of the guidelines, forming the GDG and selecting its chair, and formulating key questions in PICO format (where P is for population, I is for intervention, C is for comparator and O is for outcomes). Essential to the forming of the GDG is a process of vetting conflicts of interests. At the end of this phase, the steering group finalises the planning proposal and submits it to the Guideline Review Committee (GRC) for review and approval (Appendix 1).

In the development phase, one or more (typically external) review group(s) perform systematic reviews of the evidence for each key question and evaluate the quality of the evidence using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) methodology. Next, the steering group convenes a meeting of the GDG to formulate recommendations using the GRADE framework. Then, the steering group drafts the guidelines and conducts external peer-review.

The publishing phase starts with the submission of a final draft of the guidelines to the GRC for review and approval. Once approved, the steering group works on finalising the document (e.g. proofreading and layout) and publishing it (e.g. online and/or in print). This is typically followed by activities for dissemination, adaptation, implementation and evaluation. The steering group is expected to also have a plan for updating the guidelines.

Key steps of the guideline development process

The three key steps of the development phase are formulating the PICO questions, grading the quality of evidence and developing recommendations, as described below.

Formulating research questions using PICO

In order for guideline recommendations to be effective, they need to be clear and actionable. To achieve this goal, the process starts with specific and explicit questions that can be directly answered by the recommendations. GDGs typically build the specific and explicit questions using the PICO framework. The population represents the group targeted by the intervention being considered (i.e. those whose health outcomes will be affected by the intervention). The intervention and comparator represent the options the decision-makers (i.e. the users of the guidelines) are trying to choose. The outcomes are those that are potentially affected by the intervention and/or comparator and that are important to the population of interest and other stakeholders.

Grading the quality of evidence

The quality of evidence reflects the confidence that the estimates of effect are adequate to support a particular recommendation[8]. According to the GRADE methodology, the quality of evidence is classified in four levels: high, moderate, low and very low (Table 1). The grading is first done by each outcome of interest, then across all outcomes as a whole body of evidence[9].

The quality of evidence starts as high when it is derived from randomised trials, and as low when it is derived from observational studies. Then, the evidence may be downgraded for risk of bias[10], inconsistency[11], indirectness[12], imprecision[13] and publication bias[14]. It may also be upgraded for large magnitude of effect, a dose–response relationship, and when plausible biases would underestimate the effect[15].

Developing recommendations

While the components of a recommendation are dictated by the already developed PICO question, the main decision the GDG needs to make is about the strength and direction of the recommendation. The strength of a recommendation ('strong' or 'conditional') reflects the extent to which the GDG is confident that the desirable effects of the intervention under consideration outweigh its undesirable effects (relative to the comparator). In terms of direction, a recommendation is either in favor of or against the intervention[16]. There are, therefore, four different combinations of strength and direction: strongly in favor of intervention A over comparator B; conditionally in favor of A over B; conditionally against A over B and strongly against A over B.

In terms of implications, policy makers can adopt a strong recommendation in most situations, while they need to involve stakeholders in the decision on whether to adopt or not a conditional recommendation. According to the GRADE framework, the direction and strength of the recommendation are affected by the following factors: magnitude of the problem, values and preferences, quality of evidence, balance of desirable and undesirable outcomes, resource use, impact on equity, feasibility and acceptability[17].

Review of ITB policies

Current guidelines of the International Atomic Energy Agency (IAEA) in emergency preparedness and response related to ITB, current practice in EU countries and the experience from Japan were presented to the GDG.

IAEA

IAEA's protection strategy is defined in a number of publications, including Safety Fundamentals[18], Generic Safety Requirements (GSR) Parts 3 and 7[19, 20], Generic Safety Guide (GSG-2 and GSG-2.1)[21, 22] and a number of technical level publications (EPR series)[23]. These publications provide the basis for a justified and optimised set of protective response actions to be taken in a nuclear or radiological emergency to meet the goals of emergency response. It is important to note that these actions should be developed at the preparedness stage based on the results of hazard assessment and the potential consequences of an emergency. The process of developing the arrangements for response should involve all relevant stakeholders. More specifically, the ITB is addressed at the GSR Part 7, which prescribes provision of ITB to emergency response workers, as appropriate, if exposure due to radioactive iodine is possible. For the general public, ITB is recommended to prevent stochastic effects and a projected dose of 50 mSv for the first week since the onset of exposure is used for justifying ITB as an urgent protective action. However, this value applied for planning purposes and may not be very useful in actual emergency, when doses are not yet known and ITB should be administered prior to the actual exposure, or immediately after. To help emergency, responders to decide whether ITB is justified, there are Operational Intervention Levels (OILs) recommended in order to use the thyroid monitoring data that may be more easily available in actual emergency. For accidents occurring in NPP IAEA recommends to use 0.5 μSv/h for the children younger than 7 y and 2 μSv/h for children older than 7 y—this OIL8 justifies immediate use of the ITB in combination with other protective measure, e.g. food ban, evacuation or sheltering. For those with exceeding OIL8 dose rates, long-term follow-up and medical interventions will be justified[23]. It should be clear though that in practice the decision to implement ITB will in most cases need to be taken on the basis of model predictions, which consider elements, such as plant and meteorological conditions, population characteristics and preliminary measurement data, where applicable.

EU

The EC Directorate-General for Transport and Energy (DG TREN) implemented a survey in 2008 aiming to collect the following information:

(1) An update of the latest medical knowledge regarding the safety and efficiency of stable iodine intake in case of a nuclear emergency.
(2) An comprehensive picture of the practices in all European countries, with the aim of further informing the European national authorities and exploring ways towards a European harmonisation.

EU Member States, candidate countries, Norway and Switzerland were asked to answer a questionnaire comprising a series of questions related to their ITB arrangements: formulation and dosage, effectiveness duration, intake timing, possibility of second intake, emergency reference level (ERL), targeted population, decision-making process, link with other countermeasures, iodine storage and distribution, geographical coverage, pre-distribution area, encountered difficulties, communication arrangements (before and during an emergency) and harmonisation efforts with neighboring countries. Twenty-six answers were received out of the 32 questionnaires distributed.

Table 1. Classification of the quality of evidence according to the GRADE system.

Quality	Definition
High	The likelihood that the true effect will be substantially different is low.
Moderate	The likelihood that the true effect will be substantially different is moderate.
Low	The likelihood that the true effect will be substantially different is high.
Very low	The likelihood that the true effect will be substantially different is very high.

At the time of the survey, there were no ITB arrangements in Estonia (no NPP in the vicinity), Ireland (114 km from the closest NPP), Malta, while arrangements were in preparation in the Republic of Macedonia and Croatia. Tablet of 65-mg KI (50-mg I) is the most frequent formulation found in the EU. Finland and Spain used tablets of 130-mg KI and Poland used tablets of 32-mg KI. Potassium iodate (KIO_3) is used in UK (85-mg tablet) and the Netherlands (170-mg tablet). Regarding, the posology of KI as a function of age, the major discrepancy observed in the EU concerns people over 40–45 y in age: seven countries (Denmark, Germany, Hungary, The Netherlands, Romania, Slovenia, Sweden) do not recommend the administration of KI in adults older than this age group, in contrast with the other Member States.

Quite varied practices have been observed regarding recommended time for intake. In general, the intake is advised before the releases or as soon as possible after they start. However in some countries, the intake is recommended several hours before the beginning of the release, up to 12 hours as an optimum in the Netherlands. Important differences appear also on the duration of effectiveness. While most countries consider that iodine is effective during 24 hours after intake, some countries consider a shorter time period of 2–10 hours.

A second intake is envisaged in most countries, with a similar dosage or lower dosage than the first one, mainly in case of long-lasting release, or until food restrictions can be imposed, or if stable iodine has been taken too early. In general, a second intake is envisaged 24 hours after the first one, with some exceptions in Romania (12 hours) and Poland (2–3 d). In terms of maximum quantity to be given, only Turkey and Bulgaria mention 1 g of iodine for a total of 10 d. The other countries do not provide recommendations on this quantity.

Large differences are observed in ERLs, which vary from a thyroid dose of 10 mSv in children to 5 Gy in Lithuanian adults. Also, some countries consider the projected dose to the thyroid, whereas the avertable dose is the reference in other Member States.

Pre-distribution is implemented in 14 countries having answered the questionnaire (Belgium, Czech Republic, Finland, France, Germany, Lithuania, Luxembourg, the Netherlands, Romania, Slovakia, Sweden, Switzerland, UK) from 10 to 50 km around the NPP. Stockpiling practices are quite specific to each country (national, regional and/or local level) even though several countries have decentralised national stockpiles to the local level with a view of facing practical problems related to the time required for the distribution or delay resulting from the time required for the distribution. As an example, Switzerland has recently decided to extend to 50 km its pre-distribution radius to make sure that large cities will be provided in less than 24 h.

Finally, communication arrangements vary as well: few countries organise national campaigns and others focus their communication at the local level around NPP or deliver-specific messages to pharmacists, physicians and school teachers via diverse tools such as website or leaflets.

As an outcome of this survey, a series of recommendations was made for a better harmonisation in Europe. However, no decision has been taken so far. The main messages were

(1) to give priority to the protection of neonates, children below 18 y in age, pregnant and nursing women;
(2) to protect from inhalation pathway only, except if intake of contaminated food cannot be avoided;
(3) to recommend for planning purpose an ERL of 50 mSv as thyroid equivalent dose, assessed for the most sensitive population, for the duration of the release or for 7 d;
(4) not to have a system of age-related ERLs, provided that the ERL is appropriate for children under 18 and that the relevant planning emphasises the priority in administration to be given to these age groups;
(5) to observe a high flexibility in decision-making during an emergency (ITB is a low risk countermeasure with a potential for large benefits);
(6) to administer ITB before or just after the exposure (emergency plans should be designed to provide tablets promptly);
(7) if ITB is appropriate, to advise also sheltering and food ban, and to envisage ITB during evacuation as well;
(8) to delegate the stable iodine distribution arrangements to 24-h on duty organisations;
(9) to consider option of stable iodine pre-distribution in a radius of 5–30 km around a NPP;
(10) to position in an area of 100 km from NPP stable iodine stockpiles in all hospitals with maternity units, kindergartens and schools;

(11) to consider projected dose assessment, without taking into account protective effects of other countermeasures;
(12) to adopt the 65-mg KI tablets formulation (i.e. 50 mg iodine per tablet dividable in quarters);
(13) not to make a specific recommendation for adults over 40–45 but strongly encourage both physicians and pharmacists in the emergency planning zones to perform a preventive screening aiming at detecting possible contraindications of the iodine intake among their patients;
(14) to consider a second intake after 24 h, and when repeated administration is necessary, to limit the total dose of iodine to 1 g;
(15) to indicate production vs. expiry date in view of reducing the ITB costs on the packaging of stable iodine tablets produced for stockpiling;
(16) to organise regular pre-distribution campaigns;
(17) to develop general public information handouts or leaflets to provide appropriate information to those receiving ITB as a part of overall emergency planning;
(18) to harmonise answers to frequently asked questions across EU states;
(19) to urge countries to establish conventions with their neighboring countries to define communications channels for alerting and exchanging information in case of emergency;
(20) to analyze the interest and feasibility to implement a dedicated website at the EC level for a quick information exchange in case of emergency.

Finally, as adopting a similar ERL in European countries does not guarantee the coherence of countermeasures implemented in case of accident; the proposal that decision-making on ITB should be taken on the basis of the predicted dose assessment made by the country where the accident takes place should be considered by EU member states[7].

Fukushima experience

Just after the Great East Japan Earthquake on 11 March 2011, a huge tsunami wave had pounced upon the north-eastern coast of Japan and destroyed the power supply for cooling of the shutdown nuclear reactors, leading to an unprecedented compound nuclear disaster at the Fukushima Daiichi NPP[24]. This was a combination of natural disaster and an industrial accident that led to the public health radiation emergency.

Prior to the Fukushima accident, the National Emergency Preparedness and Response (EPR) guidelines and system already existed, including emergency protective actions based on the pre-determined projected dose criteria defining when and what kind of action such as evacuation, sheltering and ITB should be implemented[25]. However, there was no pre-distribution of stable iodine tablets prior to the accident. Following the EPR Guidelines, ITB as the protective countermeasure was recommended, when the exposures, estimated based on the released amounts, have achieved projected 10 mSv effective dose from external exposure and projected 100 mSv equivalent dose to a child's thyroid. The Nuclear Safety Commission and Authority ordered the implementation of ITB to the local government on 12 March 2011. However, due to the disrupted communications during evacuation, and primarily due to the lack of detailed arrangements, administration of stable iodine for ITB was not implemented uniformly[26]. Nonetheless, the overall response including evacuation, sheltering and control of food chain was implemented in a timely manner by the central and local governments. Consequently, internal doses to the thyroid estimated in children and in evacuees in Fukushima were quite low[27]. According to the WHO[28, 29] and UNSCEAR[30] reports, an uncertainty in dose estimates may still exist, and a small group might have a risk of thyroid cancer in the future, as it was seen in Chernobyl children. On the other hand, the risk of radiation-induced thyroid cancer in Fukushima is quite different from that in Chernobyl considering the considerable range of thyroid doses in the affected populations[31, 32]. In addition, the difference in risk can also be linked to the iodine deficient diet in Belarus at the time, which played a synergistic role for thyroid cancer risk, while for the Fukushima population, the diet is rich in iodine contained in seaweed and seafood.

The Fukushima Health Management Survey is ongoing in Fukushima[33]. Current data from the thyroid ultrasound screening programme targeting ~3 70 000 children and using high-sensitivity equipment demonstrate a certain number of thyroid micro-carcinomas, which most likely is unrelated to radiation-exposure[34]. The clinical development of papillary thyroid micro-carcinomas is quite slow, and this type of cancer is considered mostly non-aggressive. For this reason, a certain sub-type of papillary thyroid carcinoma has been recently re-classified as a non-cancer disease by the WHO's International Agency for Research on Cancer (IARC) ICD-10[35]. Moreover, there is no internationally agreed golden standard on management of thyroid micro-carcinomas, as there are both risks and benefits of the treatment to be considered. In this regard, the last American Thyroid Association guidelines[36], endorsed by several other thyroid associations, do not recommend invasive interventions at such early stages but either a non-invasive surgical treatment such as lobectomy, or an active surveillance until the evidence of growth or clinical manifestations. Therefore, the benefits of thyroid screening programmes have to be carefully considered. However, the failure of ITB countermeasure at the initial response in Fukushima has even now evoked noticeable concerns on the late occurrence of thyroid cancer.

During response to the Fukushima accident, ~17 500 stable iodine tablets (50 mg/tablet of KI) were distributed to about 2000 workers of the Tokyo

Electric Power Company (TEPCO) and contractors involved in the emergency response from 13 March to 12 October 2011[37] (including more than 10 women). Some 70% of them took 10 or less KI tablets during recovery operations on the site (the highest amount was 87 tablets). Excess intake of iodine is known to induce hypothyroidism[38]. The employer performed health check-ups by blood tests to 229 workers, because either they self-administered KI continuously for more than 14 d or received more than 20 tablets. All these workers were male and 20% of them were over 40. Notably, three workers who took 38, 48 and 48 tablets of KI, respectively, had levels of thyroid stimulating factor (TSH) greater than the normal value, and decreased levels of free thyroxine (FT4). The follow-up examination of these workers showed that hypothyroidism was transient and the levels of TSH and FT4 returned to normal values eventually. There is no consensus on the duration of KI administration in radiation emergency, as it was highlighted by Fukushima experience. On the other hand, repeated administration of KI may be necessary when there is a continuing release and a risk of inhalation or ingestion of radioactive iodine. Therefore, there is a number of open-ended issues with regard to the ITB and an appropriate protocol for the administration of KI, including its' repeated use, has to be proposed[39].

RESULTS

The GDG considered the approach to formulating future potential recommendations first and working out the PICO questions to tailor the evidence search to the proposed recommendations. The following five areas were discussed by the GDG to be addressed by the systematic reviews for the revision of the ITB guidelines:

(1) Rationale of ITB use in nuclear emergency: As ITB is a well-established emergency protective measure recommended by previous WHO guidelines and other international standards, no systematic review is needed to address the justification/rationale for ITB use.
(2) Sensitive populations: Based on the Chernobyl experience, infants and children less than 5 y of age are considered to be at highest risk for developing thyroid cancer[40]. Also pregnant and lactating women should be given priority, followed by children <14 y and adolescents <18 y. The PICO questions need to consider all these population sub-groups as part of the (P) population.
(3) Timing of KI administration: ITB is a part of the emergency protective measures and its administration is linked to and depends on availability of other measures, e.g. access to shelters. For stable iodine administration timing, such questions as ITB logistics (acquisition and access to KI stockpile, distribution and pre-distribution methods, etc.) have to be considered. As KI administration is a well-established practice worldwide[37], no systematic review is required to justify ITB per se.
(4) Dose, form and duration of stable iodine administration for continuing or repeated releases of radioactive iodine.

Information on stable iodine dosage used in different EU countries emergency plans has been reviewed and published. The KI manufacturers include this information in the insert of the KI tablet packaging. Conventionally, dosages have not been changed since 1990s. This may need to be reviewed at some point in future, as the worldwide iodine deficiency situation has improved in recent decades. Solid and liquid pharmaceutical forms of stable iodine for ITB are currently in use in different countries. When choosing the option for stockpiling, in addition to the pharmaceutical form of stable iodine, other factors such as shelf life and costs should be taken into account.

Regarding duration of administration, in case of continuous release of radioactive iodine and if evacuation is not possible, repeated use of ITB may be necessary. There are concerns about side effects of ITB for certain age groups. As it was seen from Fukushima experience, some workers self-administered up to 80 tablets of KI, and developed a transient functional thyroid dysfunction, which disappeared when KI use was interrupted[37].

When there is a risk of ingestion of radioactive iodine, food restrictions may be required in addition to ITB. In case of inhaled radioactive iodine, ITB use should not be recommended later than 48 h after exposure, as the evidence reports an increased risk due to prolonged biological half-life of radioactive iodine in such case[41, 42].

(5) Side effects. Concerning side effects of repeated administration of stable iodine, there are two primate studies on repeated KI use that showed no significant side effects[43, 44]. As seen in Fukushima emergency workers, who have been self-administering KI, demonstrated transient hyperthyroidism that returned to normal as soon as KI use was terminated.

Research questions

Based on the discussions above, the following preliminary PICOs/research questions were formulated:

PICO 1

In vulnerable population sub-groups, i.e. infants, children, pregnant or lactating women exposed continuously/repeatedly to radioactive iodine (if evacuation is impossible and/or food/water replacement is not available) (P),

does repeated ITB (I) as compared to single ITB administration (C) reduce the risk of relevant outcomes, such as thyroid cancer, hypothyroidism and benign thyroid nodules (O)?

PICO 2

In a population exposed to radioactive iodine (P), does ITB administered prior to or within the first 2 hours after the exposure (I) as compared to no ITB administration (C) reduce the risk of relevant outcomes, such as thyroid cancer, hypothyroidism and benign thyroid nodules (O)?

Further on, these review questions were seen to need more refinement in order to enable a systematic review approach to retrieve and evaluate appropriate evidence. Specifically, the intervention/exposure and comparison group definition were judged to require further revision in the framework of the review planning process.

Next steps

Systematic reviews

As a basis for the revised WHO guidelines, a systematic review addressing the evidence questions as defined by the GDG and formulated according to the PICO format will be performed. A systematic review on adverse effects of ITB[5] is available as a starting point, but this review does not address all the evidence questions to be assessed for the new guideline. A systematic review protocol has been developed, addressing the necessary steps for a state of the art systematic review[45]. The protocol contains the final review questions in PICO format. Study eligibility criteria will be somewhat broader than for systematic reviews on, e.g. clinical interventions, as the available literature is expected to be limited according to a first scoping exercise done by the review team. Extensive searches will be conducted in several bibliographic databases including Medline and EMBASE, as well as in the gray literature and in reference lists of existing guidelines and recommendations. All studies will be assessed for eligibility by at least two scientists, and data abstraction performed according to the protocol, followed by the risk of bias assessment of individual studies and a GRADE-based bias assessment of the body of evidence with regard to the different study questions. This latter part will be done in close collaboration between review authors and the GDG. Reporting along PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[46] will be provided.

Grading of outcomes

Concerning the effects of the ITB itself, both positive and negative outcomes should be looked at in various sub-populations, the risk of thyroid cancer being the most critical outcome of course. Thyroid cancer risk does not seem to increase in adults following exposure to radioiodine. Recently reported findings from Ukraine and Russia indicating an increase in thyroid cancer risk adults exposed at the age of 45–50[47], which seems inconsistent with current understanding of the radiation-induced thyroid carcinogenesis and should be interpreted with caution.

Positive outcomes of ITB are

- reduced risk of thyroid cancer,
- reduced risk of hypothyroidism at high doses of radioiodine,
- reduced risk of benign nodules.

Negative outcomes of ITB are

- transient neonatal hypothyroidism,
- autoimmune thyroiditis,
- hyperthyroidism and iodine induced thyrotoxicosis.

Iodine intolerance is also considered a negative outcome; therefore patients with hypersensitivity to iodine should be excluded from ITB administration (intolerance of iodine is a rare condition and should not be confused with X-ray contrast media allergy and seafood allergies).

Grading of strength of evidence, developing recommendations and assessing their strength and weaknesses

This part of the project was implemented at the second meeting of the GDG held in January 2016 at the Department of Endocrinology, of the University of Pisa and falls outside of the scope of this report.

The guidelines are being drafted. They will undergo the round of external peer-review, and will be finalised and published before the end of 2016.

CONCLUSION

At the first meeting in Würzburg in 2014, the revision of the WHO guidelines for ITB was re-started in compliance with the new WHO handbook for guideline development. The GDG discussed potential areas to be addressed and applied the GRADE process to draft focused questions of interest. The guideline development process will continue with discussing and finalising the PICO questions via email correspondence, rating of outcomes by the GDG and documenting the decision process. After performance of systematic reviews, the GDG will evaluate the evidence provided in a transparent approach, issue recommendations based on the evidence and draft the revised guidelines for review by an external review group before being published by WHO.

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APPENDIX

Appendix 1. The guideline development process at WHO (source: WHO).

Stage	Primary contributor	Step
Planning	WHO Member State, WHO country office or public/private entity	Request guidance on a topic.
	WHO technical unit	Determine if a guideline is needed; review existing WHO and external guidelines.Obtain approval for guideline development from the director of the relevant technical unit at WHO. Discuss the process with the GRC Secretariat and with other WHO staff with experience in developing guidelines.Form the WHO guideline steering group.Identify sufficient resources; determine the timeline.
	WHO guideline steering group	Draft the scope of the guideline; begin preparing the planning proposal.Identify potential members of the GDG and its chair. Obtain declaration of interests and manage any conflicts of interest among potential GDG members.
	WHO guideline steering group and GDG	Formulate key questions in PICO format; prioritize outcomes.
	WHO guideline steering group	Finalize the planning proposal and submit it to the GRC for review.
	GRC	Review and approve the planning proposal.
Development	Systematic review team	Perform systematic reviews of the evidence for each key question.Evaluate the quality of the evidence for each important outcome, using GRADE as appropriate.
	WHO guideline steering group	Convene a meeting of the GDG.
	GDG	Formulate recommendations using the GRADE framework.
	WHO steering group	Draft the guideline document.
	External review group	Conduct external peer review.
Publishing and updating	WHO guideline steering group and editors	Finalize the guideline document; perform copy-editing and technical editing; submit the final guideline to the GRC for review and approval
	GRC	Review and approve the final guideline.
	WHO guideline steering group and editors	Finalize the layout; proofread.Publish (online and in print as appropriate)
	WHO technical unit and program manager	Disseminate, adapt, implement, evaluate
	WHO technical unit	Update