

SHORT COMMUNICATION

Role of parenteral iron in transfusion requirements after total hip replacement. A pilot study

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SUMMARY. An important percentage of patients undergoing total hip replacement (THR) receive allogeneic blood transfusion (ABT) to avoid the risks of acute anaemia. However, concerns about the risks of ABT have led to the search for alternatives, such as stimulation of erythropoiesis.

We prospectively investigated the effect of postoperative administration of 300 mg of intravenous iron sucrose on ABT requirements in THR patients (group 2; $n = 24$). A previous series of 22 THR patients served as the control group (group 1). All patients were operated on by the same surgeon, using the same implant, and a set of clinical data was gathered.

No adverse reactions to iron administration were observed. The group-given iron showed a trend to a

lower transfusion rate (46 vs. 73%; $P = 0.067$) and lower transfusion index (0.96 vs. 1.68 units/patient; $P = 0.038$). Moreover, amongst the non-transfused patients, admission haemoglobin levels were lower in those coming from the iron group than those from the control group (12.7 ± 0.9 vs. 14.0 ± 1.2 g dL⁻¹, respectively; $P = 0.017$).

Postoperative parenteral iron administration could be a safe and effective way to reduce ABT requirements in the THR patients. A large, randomized controlled trial to confirm these results is warranted.

Key words: allogeneic blood transfusion, hospital stay, iron sucrose, postoperative infection, preoperative haemoglobin, total hip replacement.

Unilateral total hip replacement (THR) can result in a substantial blood loss resulting in 30–70% of these patients receiving allogeneic blood transfusion (ABT) (Bierbaum *et al.*, 1999; Feagan *et al.*, 2001; Rosencher *et al.*, 2003). However, allogeneic blood is a scarce and increasingly expensive resource and ABT itself is not a risk-free therapy. These drawbacks have led to the development of different methods to reduce or avoid ABT in these patients, including implementation of restrictive transfusion protocols, use of autologous blood and administration of pharmacological agents (Carless *et al.*, 2004; Scottish Intercollegiate Guidelines Network, 2004).

In this context, the administration of intravenous iron has been successfully used to accelerate

haemoglobin (Hb) level recovery and to reduce transfusion requirements after surgery for hip fracture (Cuenca *et al.*, 2004, 2005). Interestingly, postoperative infection rate was lower among iron-treated patients than among those who did not receive iron (Cuenca *et al.*, 2004, 2005). These results prompted us to investigate prospectively the effect of postoperatively administered intravenous iron sucrose on transfusion requirements and postoperative morbidity in patients undergoing surgery for THR.

MATERIALS AND METHODS

Patients and treatment

Twenty-four consecutive patients undergoing surgery for THR received 300 mg of iron sucrose postoperatively (100 mg day⁻¹, starting after surgery) (group 2). A retrospective series of 22 THR patients who did not receive iron was the control group (group 1). Patients with haematological pathology or

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coagulation disorder and those on anticoagulant therapy or with known infection or malignancy at admission were excluded. All patients gave informed consent to receive intravenous iron therapy, and the study was approved by the local ethics committee.

Surgical procedure

All patients were operated on under general anaesthesia or loco-regional anaesthesia. All surgical procedures were performed by the same surgeon, and all patients were planned to receive a cemented bipolar hip prosthesis (Elite Plus, DePuy, Leeds, UK).

Postoperative care

After the operation, all patients were admitted to the postoperative care unit for 12–24 h and then transferred to the orthopaedic ward. According to the hospital's protocol, all patients received antibiotic prophylaxis (cefuroxime: 1.500 mg intravenously 1 h before operation and 750 mg every 8 h during 2 days after the operation), postoperative analgesia (metamizol magnesium 2 g + acetaminophen 1 g in continuous perfusion every 8 h plus diclofenac sodium 75 mg intramuscularly every 12 h, for at least the first 48 postoperative hours) and antithrombotic prophylaxis adjusted doses of low molecular weight heparin from admission to the third postoperative week (nadroparin, 2850–3800 IU anti-Xa subcutaneously every 24 h). Wherever possible, THR patients were allowed to sit the day after surgery and start mobilization with walking aids 2–3 days after surgery.

Transfusion protocol

In these two groups of patients, only leucoreduced red cell concentrates were used. ABT was given when Hb level fell below 8 g dL⁻¹ and/or in the presence of symptoms of acute anaemia. Assuming that one ABT unit will raise patient's Hb level by 1 g dL⁻¹, patients received the number of blood units that were required to reach a Hb concentration of 1 g dL⁻¹ above the transfusion trigger. For symptomatic transfusion, blood units were given one-by-one until the disappearance of symptoms of acute anaemia. This transfusion protocol was uniformly applied in the operating theatre, the postoperative care unit and the ward for the entire duration of hospitalization.

Clinical variables

The analysed variables included patient's gender and age; comorbidities, including anaemia (Hb ≤12 g dL⁻¹ for women and Hb ≤13 g dL⁻¹ for men), according to WHO criteria (WHO, 1968); type of anaesthesia; perioperative and pretransfusion Hb levels; transfusion rate as percentage of patients receiving transfusion (%); transfusion index as units transfused per patient; postoperative infectious complications (urinary tract, respiratory tract and wound infections), according to the Centres for Disease Control (CDC) criteria (Horan *et al.*, 1992); adverse reaction to treatment; length of hospital stay (LHS); and in-hospital mortality.

Statistical analysis

Data were expressed as percentage (%) or as the mean ± SD (*n*). Pearson's χ^2 -test or Fisher's exact test was used for comparison of qualitative variables and Student's *t*-test for comparison of quantitative variables. Comparison of perioperative Hb levels was carried out using a repeated measures MANOVA test with a within-factor (up to five levels) and one between-factor (group). All statistics were performed with spss 11.0 (Licensed to the University of Málaga, Spain), and a *P*-value <0.05 was considered statistically significant.

RESULTS

There were no significant differences with respect to patients' age, gender distribution, comorbidities, type of anaesthesia (Table 1) or perioperative Hb levels among groups (Fig. 1; Table 1). Only six patients (four in group 1 and two in group 2) were operated on under loco-regional anaesthesia, and only four patients (two in each group, mean age 55 years) received an uncemented arthroplasty.

No iron sucrose side effects were observed in this study. ABT was given to 73% of patients in group 1 and to 46% in group 2 (*P* = 0.067) (Table 1). These differences show a 63% reduction in the relative risk of transfusion [odds ratio (OR): 0.32; 95% confidence interval: 0.08–1.28]. In addition, transfusion index in patients receiving intravenous iron was significantly lower than in those of the control group (*P* = 0.038) (Table 1).

No differences were observed between groups regarding the prevalence of anaemia [32 vs. 42%, for groups 1 and 2, respectively; *P* = non-significant (NS)] (Table 1), perioperative Hb levels (Fig. 1) or pretransfusion Hb levels (7.5 ± 0.8 vs. 7.6 ± 0.9 g dL⁻¹, for groups 1 and 2, respectively;

Table 1. Demographic and clinical data of patients undergoing surgery for total hip replacement

	Group 1	Group 2	P
Patients	22	24	
Age (years)	77 ± 10	74 ± 11	0.25*
Gender (male/female)	3/19	7/17	0.29†
Comorbidities (n, %)			
Anaemia	7 (32)	10 (42)	0.49‡
Hypertension	4 (17)	8 (33)	0.13†
Diabetes	2 (8)	0 (0)	0.22†
COPD	2 (8)	0 (0)	0.22†
Coronary disease	3 (14)	7 (29)	0.29†
Others	4 (18)	5 (21)	1.00†
Anaesthesia (G/LR)	18/4	22/2	0.40‡
Patients transfused (n, %)	16 (73)	11 (46)	0.07‡
Transfusion index (units per patient)	1.68 ± 1.17	0.96 ± 1.12	0.04*
Postoperative infection (n, %)	5 (23)	2 (8)	0.23†
In-hospital mortality (n, %)	1 (4)	0 (0)	0.49†
Length of hospital stay (days)	11.4 ± 3.4	10.1 ± 4.4	0.29*

Group 1, control; group 2, iron sucrose 300 mg; anaemia: Hb <12 g dL⁻¹ for women, Hb <13 g dL⁻¹ for men; COPD, chronic obstructive pulmonary disease; G, general; LR, loco-regional.

*Student's *t*-test.

†Fisher's exact test.

‡Pearson's χ^2 -test.

$P = \text{NS}$). However, admission Hb levels were significantly higher in non-transfused patients when compared with transfused patients in both the control group (14.0 ± 1.1 vs. 12.1 ± 1.5 g dL⁻¹, respectively; $P = 0.007$) and the iron group (12.7 ± 0.9 vs. 11.6 ± 1.5 g dL⁻¹, respectively; $P = 0.043$). In addition, among the non-transfused patients,

admission Hb levels were lower in those from the iron group than in those from the control group (12.7 ± 0.9 vs. 14.0 ± 1.1 g dL⁻¹, respectively; $P = 0.011$).

Transfusion data were reanalysed after stratifying the patients according to admission Hb level. For patients with preoperative Hb <13 g dL⁻¹, transfusion index was lower in the iron group than in the control group (2.18 ± 0.98 vs. 1.12 ± 1.17 units per patient, respectively; $P = 0.019$). For patients with preoperative Hb ≥ 13 g dL⁻¹, iron treatment did not result in a reduction of transfusion requirements (1.18 ± 1.17 vs. 0.57 ± 0.98 units per patient, respectively; $p = 0.268$) but resulted in a shorter LHS (10.8 ± 2.1 vs. 8.3 ± 1.4 days, respectively; $P = 0.012$).

There were seven postoperative infections in the entire series: four (57%) urinary tract infections, two (29%) respiratory tract infections and one (14%) surgical wound infection. Overall, there was a trend to lower postoperative infection rate in the iron group when compared with the control group (22.7 vs. 8.3% ; $P = 0.23$), but no difference was observed when comparing non-transfused patients with those who received ABT (21.1 vs. 11.1% ; $P = 0.42$). However, the three serious infections (two pneumonia and one wound infection) occurred in transfused patients in the control group. There was only one in-hospital death in the entire series: one

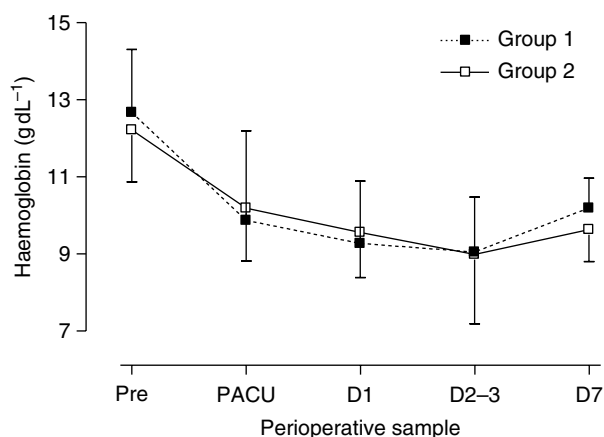


Fig. 1. Perioperative haemoglobin levels in patients undergoing surgery for total hip replacement, receiving postoperative treatment with 300 mg intravenous iron sucrose (group 2) or no treatment (group 1). Differences between groups were not significant (MANOVA test). Pre, preoperative; PACU, post-anaesthesia care unit; D, postoperative day.

patient in the control group who died on the sixth postoperative day from an acute myocardial infarction (Table 1).

DISCUSSION

To avoid possible perioperative anaemia-related complications and to reduce mortality, 30–70% of the patients undergoing THR received at least one unit of ABT (Bierbaum *et al.*, 1999; Feagan *et al.*, 2001; Rosencher *et al.*, 2003). However, ABT itself is not a risk-free therapy, and concerns about possible adverse effects in surgical patients, specially increased risk of bacterial infection (Vamvakas, 2002), have led to the use of restrictive transfusion criteria and to the search for transfusion alternatives. In this context, there is a large amount of information about transfusion alternatives in elective hip surgery, including the use of Preoperative Autologous Blood Donation (PABD), cell salvage and pharmacological agents to reduce blood loss or to stimulate erythropoiesis (Scottish Intercollegiate Guidelines Network, 2004), but the information related to the use of intravenous iron is scant and mostly focused on hip trauma surgery (Bernière *et al.*, 1998; Cuenca *et al.*, 2004, 2005).

It is well known that major surgery is followed by a systemic inflammatory response, whose humoral mediators inhibit erythropoiesis by suppressing erythropoietin production and action and by inducing a functional iron deficiency (FID) status (Biesma *et al.*, 1995; Van Iperen *et al.*, 1998; Andrews, 1999). This FID status is not corrected by oral iron (Sutton *et al.*, 2004), because intestinal iron absorption is decreased in the presence of inflammation (Fleming & Bacon, 2005). By contrast, when parentally administered, the iron-carbohydrate complexes are metabolized, the iron is released and then binds to transferrin in the plasma, and the redundant carbohydrate moiety is then cleared via the liver (MacDougall, 2000). Intravenous iron emerged as a therapeutic option for the treatment of FID in these patients, because the increased erythropoietic effect (4.5–5.5 times that of basal) of intravenous iron lasts for 7–10 days, after which the iron is sequestered by the reticuloendothelial system (Goodnough *et al.*, 2000). However, there are some concerns regarding the incidence of serious, life-threatening anaphylaxis with iron dextran reported to be 0.6–0.7%, with some fatalities, whereas for ferric gluconate and iron sucrose, these figures were 0.04 and 0.002%, respectively, with no deaths (Silverstein & Rodgers, 2004). Hypersensitivity per million doses were 8.7, 3.3 and 2.6, for iron dextran, ferric gluconate and iron sucrose, respectively (Silverstein & Rodgers, 2004).

The availability of intravenous iron preparations, such as iron sucrose, with fewer and milder side effects than iron dextran, has renewed interest in this therapy. The effectiveness of iron sucrose in the treatment of anaemia after scoliosis correction and hip trauma surgery (Bernière *et al.*, 1998; Cuenca *et al.*, 2004, 2005) prompted us to assess the safety and efficacy of 3×100 mg doses of intravenously administered iron sucrose for the treatment of acute anaemia in patients undergoing surgery for THR.

With the information obtained from previous studies in hip fracture repair (Cuenca *et al.*, 2004, 2005), we estimated the dose of iron to be administered assuming that at least 100 mg of iron is needed to raise Hb level by 1 g dL^{-1} and that perioperative blood loss would decrease the Hb level by 3 g dL^{-1} (Rosencher *et al.*, 2003). Accordingly, three doses of 100 mg of iron sucrose were administered to all patients. As expected, no side effects were observed to intravenous iron sucrose, but we found lower transfusion requirements in those who had an admission Hb level lower than 13 g dL^{-1} , whereas there were no differences in either the percentage of transfused patients or the transfusion index amongst patients with preoperative Hb $\geq 13 \text{ g dL}^{-1}$. The reduction of the transfusion index in patients receiving intravenous iron cannot be related to changes in transfusion practice, because a transfusion protocol was applied and there were no differences in pretransfusion Hb levels (7.5 ± 0.8 vs. $7.6 \pm 0.9 \text{ g dL}^{-1}$, for groups 1 and 2, respectively; $P = \text{NS}$). In addition, there were no significant differences in perioperative Hb levels between groups (Fig. 1).

The percentage of transfused patients in this study, especially in the control group (Table 1), is higher than that reported in other studies for this type of surgery (Bierbaum *et al.*, 1999; Feagan *et al.*, 2001; Rosencher *et al.*, 2003). However, in this respect, it is worth noting that the prevalence of preoperative anaemia (37%, Table 1) is higher than that reported in a series of 961 Spanish patients undergoing major elective orthopaedic surgery (21%; $P = 0.013$) (Bisbe *et al.*, 2003). In addition, 31% of the patients in the Orthopaedic Surgery Transfusion Haemoglobin European Overview study had preoperative Hb level $\leq 13 \text{ g dL}^{-1}$ (Rosencher *et al.*, 2003), whereas in our series, these figures were 50% for group 1 ($P = 0.055$) and 72% for group 2 ($P = 0.001$), and a low preoperative Hb level has been identified as an independent risk factor for transfusion in THR (Feagan *et al.*, 2001; Salido *et al.*, 2002), increasing with the severity of anaemia (OR: 2.2 for Hb $12\text{--}13 \text{ g dL}^{-1}$, 4.6 for Hb $11\text{--}12 \text{ g dL}^{-1}$ and 9.2 for Hb $<11 \text{ g dL}^{-1}$ with respect to Hb $>13 \text{ g dL}^{-1}$)

(Feagan *et al.*, 2001). Accordingly, in both groups, preoperative Hb levels were higher in non-transfused patients than in those who required ABT. However, the preoperative Hb level was 1.3 g dL^{-1} lower in non-transfused patients receiving iron sucrose than in non-transfused control patients (12.7 ± 0.9 vs. $14.0 \pm 1.1 \text{ g dL}^{-1}$, respectively; $P = 0.011$), suggesting a stimulatory effect of iron sucrose on erythropoiesis.

In our series, 10 of 24 patients treated with iron sucrose were anaemic (Table 1). According to available laboratory data (mean corpuscular volume, mean corpuscular Hb, length of erythrocyte sedimentation rate, C-reactive protein and creatinine), anaemia in these patients might be classified as iron-deficiency anaemia ($n = 2$), anaemia of chronic disease (ACD, $n = 2$), ACD plus iron deficiency ($n = 2$) and anaemia of unknown cause ($n = 4$) (Guralnik *et al.*, 2004). In addition, there were two patients with low corpuscular volume and low corpuscular Hb without anaemia (iron deficiency). Therefore, these patients would have been expected to benefit from preoperative administration of iron sucrose alone or in combination with Recombinant human erythropoietin (EPO).

In this regard, a randomized trial of iron preload prior to major joint replacement showed that anaemic patients benefit significantly from preoperative iron supplements over 4 weeks (Andrews *et al.*, 1997). In addition, iron supplementation in patients without obvious anaemia protects against a fall in Hb level during the immediate postoperative period, suggesting a widespread underlying depletion of iron stores in this group despite a normal Hb level (Andrews *et al.*, 1997). Unfortunately, at the time of this study and for most patients, scheduled time to surgery was too short and they were admitted to the hospital on the morning of the operation, thus precluding the implementation of preoperative treatment with intravenous iron. Additionally, as 65% of transfusions were given on the third or fourth postoperative day or later, an extended postoperative iron administration schedule might be useful to reduce further late postoperative ABT.

Regarding the effects of lowering transfusion rate on clinical outcomes, although the three serious postoperative infections registered in the study were in transfused patients of the control group, the difference in the postoperative infection rate between groups was not statistically significant and cannot be speculated. Similarly, the importance of the reduction in LHS in iron-treated patients with preoperative $\text{Hb} \geq 13 \text{ g dL}^{-1}$ is hard to evaluate, as the number of patients included is small and the control group represents a different time period.

In conclusion, administration of iron sucrose seems to be effective in the reduction of the requirements of ABT in THR patients. If confirmed by a large randomized clinical trial, these findings would provide a rationale to treat THR patients with intravenous iron, alone or in combination with EPO, to attain higher perioperative Hb concentrations and better early functional recovery (and perhaps to reduce the risk of postoperative infection and to shorten LHS), whilst limiting the exposure to ABT.

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REFERENCES

- Andrews, N.C. (1999) Disorders of iron metabolism. *The New England Journal of Medicine*, **341**, 1986–1995.
- Andrews, C.M., Lane, D.W. & Bradley, J.G. (1997) Iron pre-load for major joint replacement. *Transfusion Medicine*, **7**, 281–286.
- Bernière, J., Dehullu, J.P., Gall, O. & Murat, I. (1998) Intravenous iron in the treatment of postoperative anaemia in surgery of the spine in infants and adolescents. *Revue de Chirurgie Orthopedique et Reparatrice de l'appareil Moteur*, **84**, 319–322.
- Bierbaum, B.E., Callaghan, J.J., Galante, J.O., Rubash, H.E., Tooms, R.E. & Welch, R.B. (1999) An analysis of blood management in patients having a total hip or knee arthroplasty. *The Journal of Bone and Joint Surgery. American Volume*, **81-A**, 2–10.
- Biesma, D.H., Van De Wiel, A., Beguin, Y., Keraaijenhagen, R.J. & Marx, J.J.M. (1995) Post-operative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism. *European Journal of Clinical Investigation*, **25**, 383–389.
- Bisbe, E., Saez, M., Castillo, J., Mestre, C., López, R. & Castaño, J. (2003) Prevalence of anemia in elective orthopedic surgery patients: implications for blood conservation techniques. *Transfusion Alternatives in Transfusion Medicine*, **5** (Suppl. 1), 49.
- Carless, P., Moxey, A., O'Connell, D. & Henry, D. (2004) Autologous transfusion techniques: a systematic review of their efficacy. *Transfusion Medicine*, **14**, 123–144.
- Cuenca, J., García-Erce, J.A., Martínez, A.A., Solano, V.M., Molina, J. & Muñoz, M. (2005) Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair. Preliminary data. *Archives of Orthopaedic and Trauma Surgery*, **125**, 342–347.
- Cuenca, J., García-Erce, J.A., Muñoz, M., Izuel, M., Martínez, A.A. & Herrera, A. (2004) Patients with

- perthrochanteric hip fracture may benefit of preoperative intravenous iron therapy: a pilot study. *Transfusion*, **44**, 1447–1452.
- Feagan, B.G., Wong, C.J., Lau, C.Y., Wheeler, S.L., Sue-A-Quant, G. & Kirkley, A. (2001) Transfusion practice in elective orthopaedic surgery. *Transfusion Medicine*, **11**, 87–95.
- Fleming, R.E. & Bacon, B.R. (2005) Orchestration of iron homeostasis. *The New England Journal of Medicine*, **352**, 1741–1744.
- Goodnough, L.T., Skikne, B. & Brugnara, C. (2000) Erythropoietin, iron, and erythropoiesis. *Blood*, **96**, 823–833.
- Guralnik, J.M., Eisenstaedt, R.S., Ferrucci, L., Klein, H.G. & Woodman, R.C. (2004) The prevalence of anemia in persons age 65 and older in the United States: evidence for a high rate of unexplained anemia. *Blood*, **104**, 2263–2268.
- Horan, T.C., Gaynes, R.P., Martone, W.J., Jarvis, W.R. & Emori, T.G. (1992) Centres for disease control definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infection Control and Hospital Epidemiology*, **13**, 606–608.
- MacDougall, I.C. (2000) Intravenous administration of iron in epoetin-treated haemodialysis patients – which drugs, which regimen? *Nephrology, Dialysis, Transplantation*, **15**, 1743–1745.
- Rosencher, N., Kerckamp, H.E., Macheras, G., Munuera, L.M., Menichella, G., Barton, D.M., Cremers, S. & Abraham, I.L. & OSTHEO Investigation (2003) Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion*, **43**, 459–469.
- Salido, J.A., Marín, L.A., Gómez, L.A., Zorrilla, P. & Martínez, C. (2002) Preoperative hemoglobin levels and the need for transfusion after prosthetic hip and knee surgery: analysis of predictive factors. *The Journal of Bone and Joint Surgery. American Volume*, **84-A**, 216–220.
- Scottish Intercollegiate Guidelines Network. (2004). Perioperative blood transfusion for elective surgery. A national clinical guideline. Available at <http://www.sign.ac.uk>.
- Silverstein, S.B. & Rodgers, G.M. (2004) Parenteral iron therapy options. *American Journal of Hematology*, **76**, 74–78.
- Sutton, P.M., Cresswell, T., Livesey, J.P., Speed, K. & Bagga, T. (2004) Treatment of anaemia after joint replacement. *The Journal of Bone and Joint Surgery. British Volume*, **86-B**, 31–33.
- Vamvakas, E.C. (2002) Possible mechanisms of allogeneic blood transfusion-associated postoperative infection. *Transfusion Medicine Reviews*, **18**, 144–160.
- Van Iperen, C.E., Kraaijenhagen, R.J., Biesma, D.H., Beguin, Y., Marx, J.J.M. & Van de Wiel, A. (1998) Iron metabolism and erythropoiesis after surgery. *The British Journal of Surgery*, **85**, 41–45.
- World Health Organisation. (1968) *Nutritional Anemias: Reports of a WHO Scientific Group*. World Health Organisation, Geneva.