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The impact of the AO Foundation on fracture care: An evaluation of 60 years AO Foundation

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ABSTRACT

Objectives: Sixty years ago, the Association of Osteosynthesis (AO) was founded with the aim to improve fracture treatment and has since grown into one of the largest medical associations worldwide. Aim of this study was to evaluate AO's impact on science, education, patient care and the MedTech business.

Design/methods: Impact evaluations were conducted as appropriate for the individual domains: Impact on science was measured by analyzing citation frequencies of publications promoted by AO. Impact on education was evaluated by analyzing the evolution of number and location of AO courses. Impact on patient care was evaluated with a health economic model analyzing cost changes and years of life gained through the introduction of osteosynthesis in 17 high-income countries (HICs). Impact on MedTech business was evaluated by analyzing sales data of AO-associated products.

Results: Thirty-five AO papers and 2 major AO textbooks are cited at remarkable frequencies in high ranking journals with up to 2000 citations/year. The number of AO courses steadily increased with a total of 645′000 participants, 20'000 teaching days and 2'500 volunteer faculty members so far. The introduction of osteosynthesis saved at least 925 billion Swiss Francs [CHF] in the 17 HICs analyzed and had an impact on avoiding premature deaths comparable to the use of antihypertensive drugs. AO-associated products generated sales of 55 billion CHF.

Conclusion: AO's impact on science, education, patient care, and the MedTech business was significant because AO addressed hitherto unmet needs by combining activities that mutually enriched and reinforced each other.

Introduction

Sixty years ago, a group of 13 visionary Swiss surgeons founded the Association of Osteosynthesis (AO) with the aim of improving fracture care [1]. At the time, most surgeons viewed osteosynthesis with suspicion because it was technically demanding and involved the risk of infection, so it was deemed too risky. The mainstay of fracture treatment consisted of conservative treatment. Fractures were treated with plaster casts and/or in traction so that patients were immobilized over many weeks. Typical sequelae consisted of muscle atrophy, stiff joints, loss of range of motion, and often subsequent invalidity [2].

The founders of AO believed that fracture treatment could be improved by treating patients operatively. They developed treatment guidelines stipulating "restoration of the anatomy, stable fracture fixation, preservation of blood supply and early pain-free mobilization of limb and patient" [3]. According to AO's original bylaws, promotion of osteosynthesis should be achieved by studying issues involving bone fracture treatment, experimental research, and the exchange of practical and scientific experience related to osteosynthesis [3].

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The endeavor was successful. Today, osteosynthesis has become the standard treatment for most fractures in adults and AO has grown into a global non-profit organization with over 20′000 members [1].

So far, no structured analysis has been performed to assess the impact of the actions defined in the original bylaws and their possible economic effects. On the occasion of the 60th anniversary of AO, we initiated a collaboration with the Winterthur Institute of Health Economics (WIG) [4], selected after an open call for the project, to evaluate AO's impact on the scientific community and education, on patient care from a health economic perspective, as well as on the MedTech business. The funding for the study was provided by AO as well as WIG.

Methods

Impact on the scientific community

To evaluate AO's impact on the scientific community, we analyzed the key book and journal publications brought forward by AO in the time since its foundation.

Citation frequencies of these publications in journals with high impact factors (IFs) were extracted from InCites, [5] which uses citation data from Web of Science [6]. Thresholds for the IFs were set depending on the field of research, i.e., for pre-clinical research only journals with an IF of >4 were considered, whereas for papers on clinical topics, the IF needed to be >3.

Journal publications were only included if they had been published before 2017 and were cited at least 6 times.

To determine "highly cited papers" and "hot papers", thresholds from InCites were applied. Papers are deemed "highly cited" if they receive a number of citations that brings them to the top 1% of papers in the respective research field published in the specified year. "Hot papers" are papers published in the past 2 years that received a number of citations in the most recent two-month period that places them in the top 0.1% of papers in the same field. Citation frequencies were analyzed separately for books, papers on pre-clinical topics, and papers on clinical topics.

Additionally, the development of the funding for the different areas of AO's research was analyzed.

Impact on education

AO's impact on education was evaluated by analyzing the evolution of the courses held by AO over time. The number of courses offered in different locations, the number of faculty members, as well as the number of participants registered was determined from AO's archives. An overview about AO's further educational activities was generated and its utilization was quantified.

Impact on patient care

The direct impact of AO on patient care is difficult to measure. However, since it was AO who disseminated the knowledge about how to successfully implement osteosynthesis (OS), the impact of OS is a suitable proxy for AO's impact on fracture care. Therefore, decision tree models were developed to calculate the differences in direct costs and productivity after treatment with OS compared to conservative treatment (CONS), assuming a hypothetical absence of OS, for the 3 index bones femur, tibia and radius. These 3 index bones were selected as they include frequent fracture locations of the upper and lower extremities and have specifically profited from AO innovations. Additionally, years of life gained (YLG) were calculated for femur and tibia fractures in analogy to the years of life lost (YLL) concept of the Global Burden of Disease Study [7].

Input data were derived from Swiss real-world databases and extrapolated to 16 other high-income countries[1] (HICs). Costs were summed up for the time from AO's inception in 1958 up to 2017. Based on data availability, the analysis primarily considered the working population, i.e. patients < 65 years. For proximal femur fractures, an additional analysis considering patients ≥ 70 years was performed because these fractures constitute a considerable and increasing disease burden in HICs [8–10]. These models are currently getting prepared for publication and a summary of the key results is presented herein.

Impact on the MedTech business

Using archival sources of the Synthes AG Chur on royalty payments by the various AO producers and – for the time from 1975 onwards – complemented by historical sales figures provided by DePuy Synthes, we generated an overview about the development of AO's links to the MedTech business and estimated aggregate sales figures of products developed by AO since the very beginning of the AO.

Results

Impact on the scientific community

Developing the first edition of the "Manual of internal fixation" in 1963 [11] and later the "Comprehensive classification of fractures of long bones" [12] formed the bedrocks of AO's ongoing impact on the scientific community. The current editions and successors [11–22] of these publications are still cited at remarkable frequencies today. Between 2011 and 2016, the citation frequencies of the "Manual of Internal Fixation" [13–16,20,22] and its predecessor [11] and successors [17,18] were over 1800 times/year and of the "Comprehensive Classification of Fractures of Long Bones" [12,21] over 2000 times/year.

While the initial activities of AO focused on standardizing fracture treatment, soon pre-clinical research in cell and animal models and in material sciences was promoted. Fig. 1 depicts the citation frequencies of AO papers on pre-clinical topics [23–45] between 2011 and 2016. One of these papers even met the criteria of a "hot paper" [30].

Before long, research efforts were expanded to include clinical research. Driven by the change in mindset concerning evidence-based medicine, clinical research steadily gained importance. While in 2013, pre-clinical research received approximately twice the funds of clinical research, nowadays the funds for pre-clinical and clinical research are nearly equal. Today, AO invests approximately CHF 25 million for pre-clinical and clinical research annually. This had a substantial effect on citation frequencies of publications on clinical topics [46–57] (Fig. 2).

Of note, AO's impact on the scientific community is not limited to publications. AO's research institute (ARI) focuses on pre-clinical research and development and publishes its own journal (European Cells & Materials, eCM), which also hosts a yearly conference and has held an IF ≥ 4.0 in 8 of the 10 years since it was first classified in the Citation Index.

[1] Germany[$], Austria, Belgium, The Netherlands, Luxemburg, United Kingdom, Denmark, Norway, Sweden, Finland, US, Canada, Japan, Korea[§], Australia, New Zealand, [$]Federal Republic of Germany and German Democratic Republic combined for the time before 1989 [§] Korea only since 2000, when it became an OECD high income country

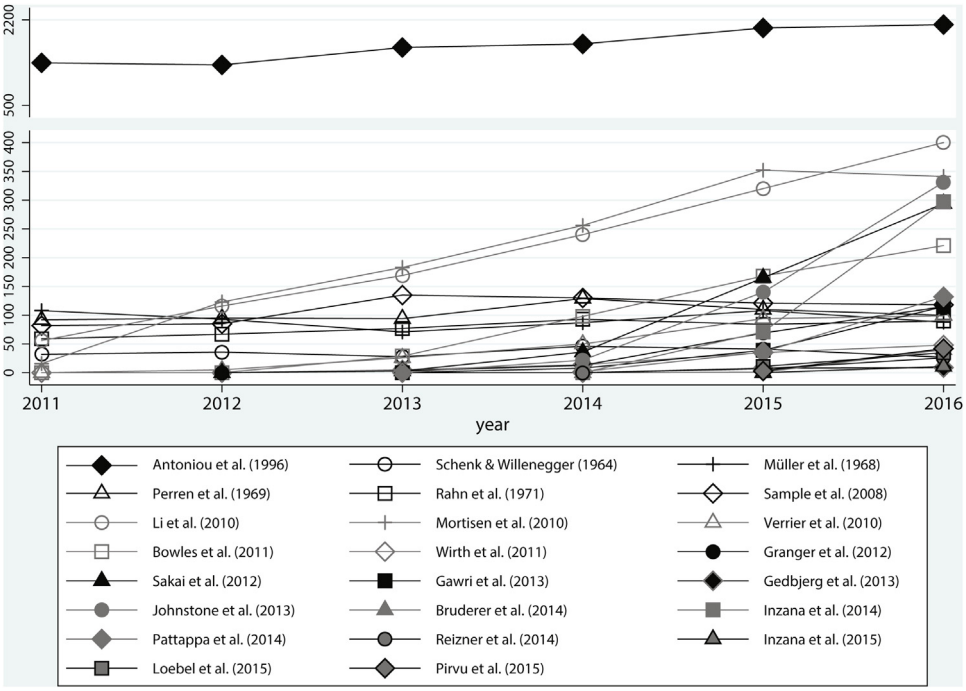

Fig. 1. Citation frequencies of papers on pre-clinical topics in journals with an IF > 4, 2011–2016.

AO's impact on education

Davos courses

Shortly after AO was founded, the first instructional courses were held in Davos.

The "Davos Courses" are still AO's flagship educational activity. The aim of the courses is to impart knowledge theoretically and practically. Thus, an important part of the courses is the "hands-on" training, offering surgeons the opportunity to use the specific implants and instruments on sawbones or human specimens.

The first of these courses took place in December 1960 with 66 participants. Quickly, the courses gained popularity in the international community – almost 90% of participants came from abroad. In 1969, the number of participants had already risen to 530 and this trend continued (Fig. 3).

The number of course participants between 1960 and 2016 sums up to approximately 65′000.

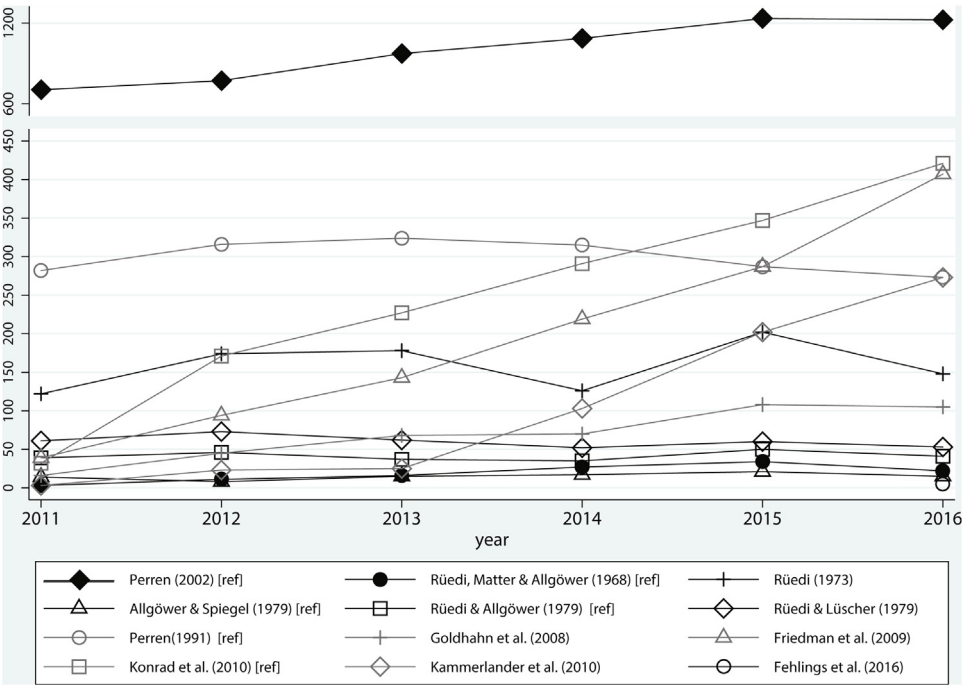

Fig. 2. Citation frequencies of papers on clinical topics in journals with an IF > 3, 2011–2016.

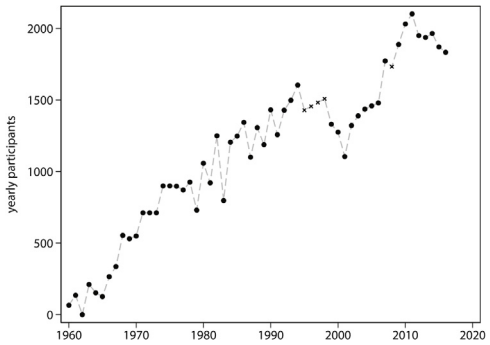

Fig. 3. AO "Davos Courses" participations 1960 to 2016. Included are courses from all divisions, as well as "special courses" and "symposia". The years 1995-98 with missing data and 2008 with an unexplainable outlier were imputed using a polynomial regression function (marked with "x"). Data source: Schneider R [60], Schneider R [61], Claudio Gubser, AO, HSG.

Worldwide courses

Soon after having established the "Davos courses" in Switzerland, AO started to organize local AO courses throughout the world. Despite the "Davos courses" being the main educational activity, the worldwide courses played an important role in the dissemination of AO techniques and in fostering the worldwide AO network.

The first AO course outside Switzerland was held in Germany in 1965, followed by Yugoslavia in 1968, Canada in 1969, and Austria as well as the US in 1970. Based on the great success, courses usually continued to be held on a regular basis once they had been introduced into a country. Courses increased steadily so that by 1994, AO had held courses in 62 countries other than Switzerland. Fig. 4 shows the introduction of AO courses between 1960 and 1994 by country.

The number of worldwide AO courses increased continuously. After the millennium it exceeded 200 courses with 10′000 participants per year (Fig. 5).

In 2016, AO held 727 courses with 45′000 participants worldwide, excluding the Davos courses.

In total, up to today, AO has held approximately 8′700 courses worldwide with 580′000 participants. Assuming an average course duration of 2.5 days, this translates into 20′000 teaching days, which were delivered by 2′500 volunteer faculty members [58].

Other educational materials and activities

Nowadays, many educational materials are available online.

On one hand, the AO Surgery Reference webpage, which contains detailed instructions for the complete surgical management process for all fractures of any given anatomical region, is a tool that is used by many surgeons worldwide. By early 2017, the reference webpage had about 40′000 returning visitors per month. In 2010, the corresponding mobile app was introduced, which has been downloaded between 6′000 and 8′000 times per month since 2013. In the first quarter of 2017, it was accessed by approximately 140′000 users per month.

On the other hand, videos, webinars and other online courses are available on a wide array of topics. The most recent development is a training program that focuses on research methodology for clinicians, the AOPEER (Program for Education and Excellence in Research). This program consists of both online resources and face-to-face training modules to provide the appropriate knowledge for surgeons to conduct high quality clinical research.

Fellowships

Another important way of training surgeons is the fellowship program, granting individual surgeons scholarships at AO hospitals, i.e., hospitals where experienced AO-affiliated surgeons are working. The fellows participate in all daily activities and observe or can even scrub-in on operations. This immersion allows them to learn the application of AO techniques including their correct indications directly from highly qualified experts, and thus guarantees for a learning experience that goes far beyond the lectures and the practical exercises during the courses.

Introduced in 1971, by 1974 already 86 fellows had taken part in the program that was first hosted by Swiss hospitals only, and subsequently expanded rapidly. From 1990 onwards, approximately 200 surgeons participated each year. Recently, these numbers have risen further to 296 participants in 2015, hosted by 130 hospitals all over the world (Fig. 6). Up to today, approximately 7′800 surgeons have participated in clinical fellowship programs.

To complement the practical training, in 2005, the AO Clinical Investigation and Documentation (AOCID) institute established a fellowship program to provide training and experience in clinical research. Participants spend 3 months full time at AOCID and are coached by a methodological mentor to complete their own clinical research project(s). Up to now, AOCID hosted 35 research fellows.

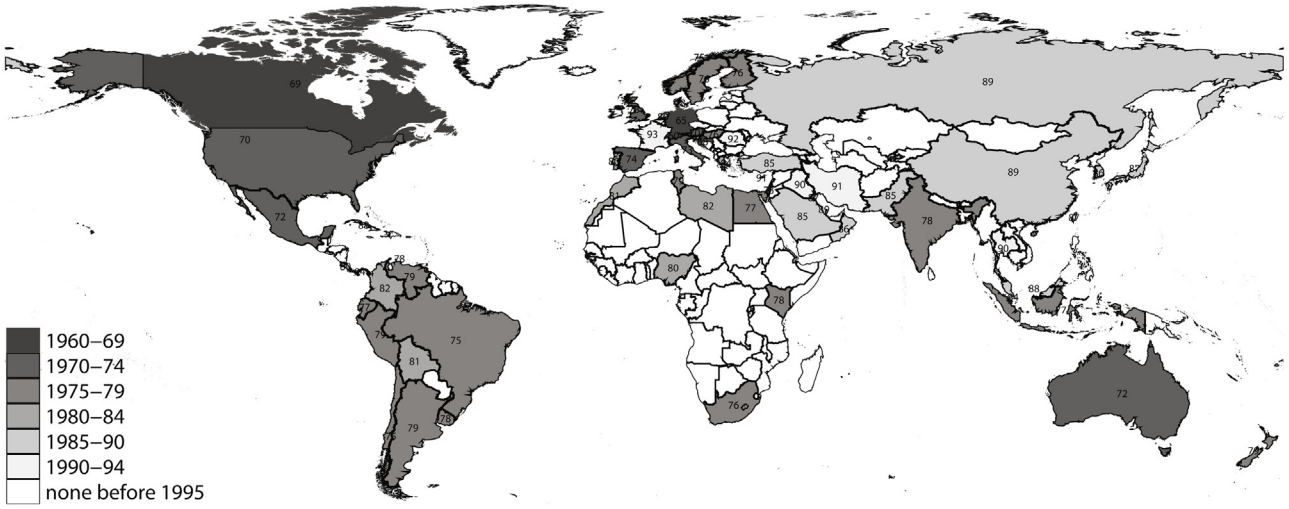

Fig. 4. Year of first AO course (up to 1994) by country. Dark colors indicate an early introduction, light colors a late introduction. Data source: Schlich T [62], Schneider R [61].

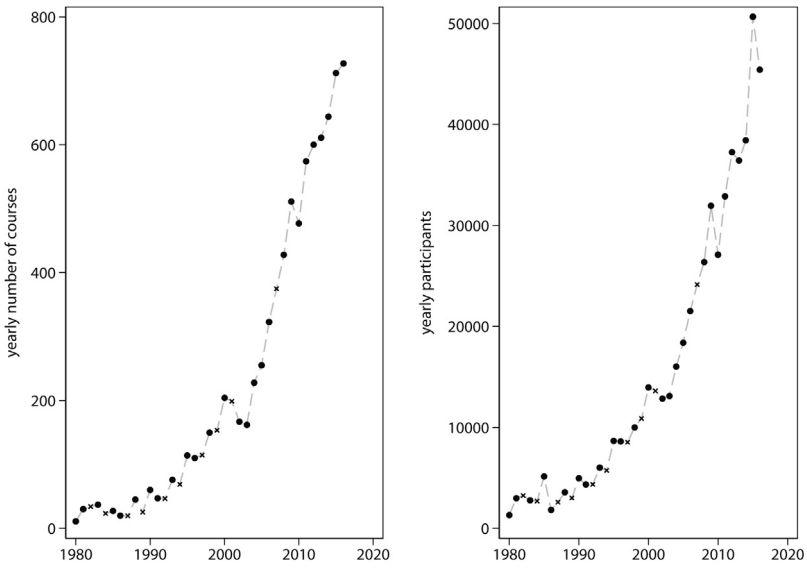

Fig. 5. Yearly number of AO courses (left) and participants (right) 1980 to 2016 worldwide (excluding Davos courses). Included are courses for surgeons from all divisions, "special courses", seminars, symposia, and, from 2008 onwards, webinars. Missing data (marked with "x") were imputed using a polynomial regression function. Data source: Claudio Gubser, AO, AO Community Development Managers.

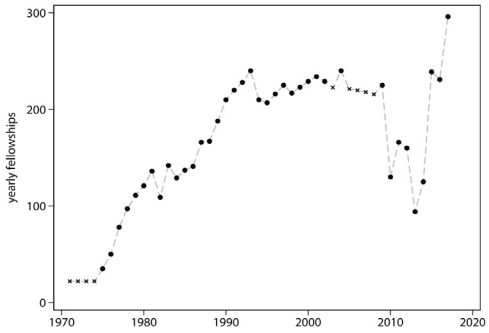

Fig. 6. Yearly AO fellowships 1971–2017. For the years marked with "x" only aggregate data (1971–1974) or no data (2003–2008) is available. Missing data were imputed using a polynomial regression function (marked with "x"). For the years 2010 onwards, only trauma-fellowships are reported due to lacking data for other divisions. Data source: Schlich T [62], Schneider R [61], AO Annual reports, AO Community Development Managers.

Impact on patient care

Modeling total cost differences between OS and CONS for the 3 index bones femur, tibia and radius demonstrated that in all these fractures, OS resulted in significant savings (Table 1). This was highest in leg fractures of the working age population (femur: Swiss Francs [CHF] 131′000/patient, tibia: CHF 104′000/patient), primarily due to the significant indirect costs caused by prolonged absence from work inherent in CONS. Of note, even when only direct costs were considered, treating these fractures operatively would be less expensive than conservatively. In contrast, the direct costs for treating radius fractures operatively exceed those of CONS by CHF 4′500 per patient, still resulting in overall savings of CHF 13′700/patient.

Extrapolating these figures to 17 HIC (including Switzerland), the use of OS in femur, tibia and radius fractures alone led to savings of CHF 925 billion over the last 60 years.

The analysis of YLG was also clearly in favor of OS (Table 2). It was estimated that the introduction of OS to treat femoral and tibial fractures resulted in a total of 77.6 million YLG in the 17 HICs analyzed. Translating these figures into premature deaths avoided in the US alone in 2001 shows that treating femur and tibia fractures in patients < 65 years with OS saved 2′600 lives and treating proximal femur fractures with OS in patients ≥ 70 years saved 126′000 lives.

Impact on the MedTech business

In addition to its educational and research activities, which enabled developing innovative yet reliable OS products, AO supervised production, marketing and sales of the latter and got in contact with potential manufacturers right in its beginnings. They established the non-profit company Synthes AG in Chur, which received all current and future intellectual property rights for instruments and implants developed by AO. In exchange to royalty payments, the Synthes AG granted exclusive production rights to Mathys and Straumann, who were the first to produce and sell AO equipment under the "Synthes" brand.

Table 1
Savings through the introduction of osteosynthesis.1958–2017.

Fracture location	Savings in Switzerland direct costs [CHF] per patient	Savings in Switzerland indirect costs [CHF] per patient	Savings in Switzerland total costs [CHF] per patient	Savings in Switzerland total costs [CHF]	Savings in USA total costs [CHF]	Savings in 17 HICs* total costs [CHF]
Femur, age <65	4'000	127'000	131'000	5 billion	122 billion	272 billion
Proximal femur, age ≥ 70	3'000	Not included in calculation (retired)	3'000	1.1 billion	32 billion	69 billion
Tibia, age <65	2'000	102'000	104'000	9.8 billion	223 billion	507 billion
Radius, age <65	−4'500	18'200	13'700	1.5 billion	30 billion	77 billion

Costs are in Swiss Francs (CHF); official 2017 conversion rate to US$: 1.026; source: https://www.exchange-rates.org/Rate/USD/CHF/12-31-2017.
* Switzerland, Germany[$], Austria, Belgium, The Netherlands, Luxemburg, United Kingdom, Denmark, Norway, Sweden, Finland, US, Canada, Japan, Korea[§], Australia, New Zealand, [$]Federal Republic of Germany and German Democratic Republic combined for the time before 1989 [§] Korea only since 2000, when it became an OECD high income country.

Table 2
Years of life gained (YLG) through the introduction of osteosynthesis 1958–2017. LYG are calculated based on the statistical life expectancies of the respective populations.

Fracture location	Total YLG in Switzerland	Total YLG in USA	Total YLG in 17 HICs*
Femur, age <65	40'000	929'000	2.5 million
Proximal femur, age ≥ 70	0.9 million	29 million	73 million
Tibia, age <65	37'000	758'000	2.1 million

* Switzerland, Germany[$], Austria, Belgium, The Netherlands, Luxemburg, United Kingdom, Denmark, Norway, Sweden, Finland, US, Canada, Japan, Korea[§], Australia, New Zealand, [$]Federal Republic of Germany and German Democratic Republic combined for the time before 1989 [§] Korea only since 2000, when it became an OECD high income country.

Synthes brand sales, which comprised products manufactured and sold by various producers, increased exponentially over time and were not only a reliable source for funding AO's activities but also generated a large international business. From 1958–2017, overall Synthes brand sales amounted to approximately CHF 55 billion.

Discussion

Impact on the scientific community

AO furthered a high number of publications with high citation frequencies. Figures show that the early books "The Comprehensive Classification of Fractures of Long Bones" [12] and "The Manual of Internal Fixation" [16] and two journal publications from the nineties and 2000s are still highly relevant today. Furthermore, numerous more recent pre-clinical and clinical papers have been and are cited at high frequencies. Increasing numbers of papers have been published in high impact journals and many of them have received high citation rankings.

The main limitation of this analysis is that no figures are available to illustrate the proportional contribution of AO compared to the total of publications in a given research field. Notwithstanding, many AO papers are ranked as "highly cited" or even "hot paper". These proportional measures indicate the importance of AO's contributions relative to other papers in the research field.

Impact on education

The aim of AO courses has always been to disseminate knowledge along with practical skills in fracture treatment and has more recently been complemented with education in research methodology. As demonstrated by the increasing number of courses held in various parts of the world and rising numbers of participants, this was perceived well in the community. The ever-growing popularity of the AO courses suggests that they satisfied previously unmet needs. AO courses are nowadays CME accredited in many countries; in some countries, attendance of one or more AO courses is even compulsory for board certification of orthopedic surgeons [58]. Experts estimate that if AO were put together as a full-blown medical school, it would, at a minimum, equal a medium-sized institution [58].

Additionally, AO's increased activities in low- and middle-income countries play an important role in providing advanced education in regions where appropriate medical training is a scarce resource.

Impact on patient care

In our impact evaluation we used the effect of the technology "osteosynthesis" as a proxy for AO's impact on patient care.

To assess cost savings, we used combined estimates (femur, tibia and radius fractures in the population age <65 years and proximal femur fractures in patients aged ≥ 70). This showed that in 17 HICs alone, introduction of the technology OS resulted in a potential net benefit of 925 billion CHF and 77.6 million YLG over the last 60 years. Not many studies have evaluated the impact of medical innovations of a similar magnitude. One of these studies assessed the impact of antihypertensive drugs in the US by quantifying the number of premature deaths avoided [59]. The study estimated that treatment with antihypertensive drugs saved 86′000 lives in the population aged 30–79 years in 2001. We estimated for the same time frame, that OS in the US avoided 2′600 premature deaths in persons < 65 years and 126′000 premature deaths in persons ≥ 70 years.

The main limitation of our approach is that the modeling is based on several assumptions and simplifications. However, appropriate measures including various sensitivity analyses were taken to test the robustness of our estimations. Overall, the underlying assumptions were rather conservative, e.g., we only included 3 index bones in 17 HICs and indirect costs of unpaid work were not considered. Thus, the overall impact of OS is likely to be even bigger. Additionally, the AO founders were not the first surgeons believing in the benefits of OS. Others such as Lambotte, Danis or Küntscher also propagated the idea of treating fractures with OS, even though their ideas and efforts did not gain a comparable spread. It seems possible that another organization may have formed and stepped into the breach to further develop and promote the technology. Nowadays, several large manufacturers provide OS products developed independently of AO or Synthes. It is impossible, however, to tell whether or how long it would have taken for OS to gain a comparable spread around the world without AO's efforts that comprised the exceptional combination of research, education and manufacturing.

Impact on MedTech business and synergistic effects

AO's involvement in the Synthes brand allowed the manufacturers to grow rapidly and generate a large international business. Synthes branded products alone, generated sales of approximately CHF 55 billion since AO's foundation. The combination of activities leading up to this was unique. High quality research formed the basis to develop successful surgical techniques, corresponding implants and instruments as well as training on how to use these in theory and practice.

Conclusion

In the 60 years since its inception, AO has grown from a small Swiss association comprising a handful of pioneer surgeons into a globally active foundation with over 20′000 members worldwide.

Our analysis shows that AO's impact on science, education, patient care, and finally the MedTech business was significant. This was only possible because AO addressed hitherto unmet needs by combining activities that mutually enriched and reinforced each other. In doing so, AO furthered the safe and effective use of OS, which led to a paradigm shift in fracture treatment and ultimately improved patient care all over the world.

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Declaration of competing interest

Alexander Joeris and Eberhard Denk are employees of the AO Foundation. Nikolaus Renner is Immediate Past President of the AO Foundation and Felix Gutzwiller has received personal fees from the AO Foundation (advisory board). Urs Brügger, Klaus Eichler, Marc Höglinger, Fabio Knöfler and Flurina Meier are employees of WIG, which has received a grant from the AO Foundation. Klaus Eichler has also received personal fees from the AO Foundation to attend an expert meeting. The other authors have nothing to disclose.

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References

[1] Jeannet J-P. A brief overview of the AO organization (chapter 3). Leading a Surgical Revolution the AO Foundation – Social Entrepreneurs in the Treatment of Bone Trauma. Cham: Springer Nature Switzerland; 2019. p. 15–9.
[2] Jeannet J-P. Treatment of bone fractures prior to 1960 (chapter 4). Leading a Surgical Revolution The AO Foundation Social Entrepreneurs in the Treatment of Bone Trauma. Cham: Springer Nature Switzerland; 2019. p. 21–31.
[3] Jeannet J-P. AO Formulates Its Credo (Chapter 8). Leading a Surgical Revolution The AO Foundation – Social Entrepreneurs in the Treatment of Bone Trauma. Cham: Springer Nature Switzerland; 2019. p. 61–72.
[4] Winterthurer Institut für Gesundheitsökonomie (WIG), Zürcher Hochschule für Angewandte Wissenschaften (ZHAW). https://wwwzhawch/de/sml/institute-zentren/wig/.
[5] Clarivate analytics. InCites.
[6] Clarivate analytics. Web of Science.
[7] Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med 2013;369:448–57.
[8] Flikweert ER, Wendt KW, Diercks RL, Izaks GJ, Landsheer D, Stevens M, et al. Complications after hip fracture surgery: are they preventable? Eur J Trauma Emergency Surg 2018;44:573–80.
[9] Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799–809.
[10] Suhm N, Kaelin R, Studer P, Wang Q, Kressig RW, Rikli D, et al. Orthogeriatric care pathway: a prospective survey of impact on length of stay, mortality and institutionalisation. Arch Orthop Trauma Surg 2014;134:1261–9.
[11] Müller ME, Allgöwer M, Willenegger H. Technik der operativen Frakturenbehandlung. 1 ed. Berlin, Heidelberg: Springer; 1963.
[12] Müller ME, Nazarian S, Koch P, Schatzker J. The comprehensive classification of fractures of long bones. Berlin, Heidelberg: Springer; 1990.
[13] Müller ME, Allgöwer M, Willenegger H. Manual der Osteosynthese. AO-Technik. 1 ed. Berlin, Heidelberg: Springer; 1969.
[14] Müller ME, Allgöwer M, Willenegger H. Manual of internal fixation. Technique recommended by the AO-group Swiss Association for the study of internal fixation: ASIF. 1 ed. Berlin, Heidelberg: Springer; 1970.
[15] Müller ME, Allgöwer M, Schneider S, Willenegger H. Manual of internal fixation. Techniques recommended by the AO Group. 2 ed. Berlin, Heidelberg: Springer; 1979.
[16] Müller ME, Allgöwer M, Schneider R, Willenegger H. Manual of internal fixation. Techniques recommended by the AO-ASIF Group. 3 ed. Berlin, Heidelberg: Springer; 1991.
[17] Rüedi TP, Murphy WM. AO principles of fracture management. 1 ed. Stuttgart, New York: Thieme; 2000.
[18] Rüedi TP, Buckley RE, Moran CG. AO principles of fracture management. 2 ed. Stuttgart, New York: Thieme; 2007.
[19] Buckley RE, Moran CG, Apivatthakakul T. AO principles of fracture management. 3 ed. Stuttgart, New York: Thieme; 2018.
[20] Müller ME, Allgöwer M, Schneider R, Willenegger H. Manual der Osteosynthese. AO-Technik. 2 ed. Berlin, Heidelberg, New York: Springer; 1977.
[21] Müller M, Nazarian S, Koch P. Classification AO des fractures - les os longs. 1 ed Berlin: Springer-Verlag; 1987.
[22] Müller ME, Allgöwer M, Schneider R, Willenegger H. Manual der Osteosynthese. AO Technik. 3 ed. Berlin, Heidelberg: Springer; 1992.
[23] Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. J Clin Invest 1996;98:996–1003.
[24] Bowles RD, Gebhard HH, Hartl R, Bonassar LJ. Tissue-engineered intervertebral discs produce new matrix, maintain disc height, and restore biomechanical function to the rodent spine. Proc Natl Acad Sci USA 2011;108:13106–11.
[25] Bruderer M, Richards RG, Alini M, Stoddart MJ. Role and regulation of RUNX2 in osteogenesis. Eur Cell Mater 2014;28:269–86.
[26] Czekanska EM, Ralphs JR, Alini M, Stoddart MJ. Enhancing inflammatory and chemotactic signals to regulate bone regeneration. Eur Cell Mater 2014;28:320–34.
[27] Gawri R, Antoniou J, Ouellet J, Awwad W, Steffen T, Roughley P, et al. Best paper NASS 2013: link-N can stimulate proteoglycan synthesis in the degenerated human intervertebral discs. Eur Cell Mater 2013;26:107–19 discussion 19.
[28] Gedbjerg N, LaRosa R, Hunter JG, Varrone JJ, Kates SL, Schwarz EM, et al. Anti-glucosaminidase IgG in sera as a biomarker of host immunity against Staphylococcus aureus in orthopaedic surgery patients. J Bone Joint Surg Am 2013;95:e171.
[29] Granger N, Blamires H, Franklin RJ, Jeffery ND. Autologous olfactory mucosal cell transplants in clinical spinal cord injury: a randomized double-blinded trial in a canine translational model. Brain: J Neurol 2012;135:3227–37.
[30] Inzana JA, Olvera D, Fuller SM, Kelly JP, Graeve OA, Schwarz EM, et al. 3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration. Biomaterials 2014;35:4026–34.
[31] Inzana JA, Trombetta RP, Schwarz EM, Kates SL, Awad HA. 3D printed bioceramics for dual antibiotic delivery to treat implant-associated bone infection. eCM: eCM Meeting Abstracts 2015, Collection 5. p..
[32] Johnstone B, Alini M, Cucchiarini M, Dodge GR, Eglin D, Guilak F, et al. Tissue engineering for articular cartilage repair–the state of the art. Eur Cell Mater 2013;25:248–67.
[33] Li Z, Kupcsik L, Yao SJ, Alini M, Stoddart MJ. Mechanical load modulates chondrogenesis of human mesenchymal stem cells through the TGF-beta pathway. J Cell Mol Med 2010;14:1338–46.
[34] Loebel C, Czekanska EM, Bruderer M, Salzmann G, Alini M, Stoddart MJ. In vitro osteogenic potential of human mesenchymal stem cells is predicted by Runx2/Sox9 ratio. Tissue Eng Part A 2015;21:115–23.
[35] Mortisen D, Peroglio M, Alini M, Eglin D. Tailoring thermoreversible hyaluronan hydrogels by "click" chemistry and RAFT polymerization for cell and drug therapy. Biomacromolecules 2010;11:1261–72.
[36] Muller J, Schenk R, Willenegger H. [Experimental studies on the development of reactive pseudarthroses on the canine radius]. Helv Chir Acta 1968;35:301–8.
[37] Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, et al. CCL5/RANTES is a key chemoattractant released by degenerative intervertebral discs in organ culture. Eur Cell Mater 2014;27:124–36 discussion 36.
[38] Perren SM, Huggler A, Russenberger M, Allgöwer M, Mathys R, Schenk R, et al. The reaction of cortical bone to compression Reaktion der Kortikalis auf Kompression. Acta Orthop Scand Suppl 1969;19–28.
[39] Pirvu T, Blanquer SB, Benneker LM, Grijpma DW, Richards RG, Alini M, et al. A combined biomaterial and cellular approach for annulus fibrosus rupture repair. Biomaterials 2015;42:11–9.
[40] Reizner W, Hunter JG, O'Malley NT, Southgate RD, Schwarz EM, Kates SL. A systematic review of animal models for Staphylococcus aureus osteomyelitis. Eur Cell Mater 2014;27:196–212.
[41] Sakai D, Nakamura Y, Nakai T, Mishima T, Kato S, Grad S, et al. Exhaustion of nucleus pulposus progenitor cells with ageing and degeneration of the intervertebral disc. Nat Commun 2012;3:1264.
[42] Sample SJ, Behan M, Smith L, Oldenhoff WE, Markel MD, Kalscheur VL, et al. Functional adaptation to loading of a single bone is neuronally regulated and involves multiple bones. J Bone Mineral Res 2008;23:1372–81.
[43] Schenk R, Willenegger H. (On the histology of primary bone healing.). Langenbecks ArchKlinChir VerDtschZChir 1964;308:440–52.
[44] Verrier S, Meury TR, Kupcsik L, Heini P, Stoll T, Alini M. Platelet-released supernatant induces osteoblastic differentiation of human mesenchymal stem cells: potential role of BMP-2. Eur Cell Mater 2010;20:403–14.
[45] Wirth AJ, Goldhahn J, Flaig C, Arbenz P, Muller R, et al. Implant stability is affected by local bone microstructural quality. Bone 2011;49:473–8.
[46] Allgower M, Spiegel PG. Internal fixation of fractures: evolution of concepts. Clin Orthop Relat Res 1979;26–9.

[47] Fehlings MG, Nater A, Tetreault L, Kopjar B, Arnold P, Dekutoski M, et al. Survival and clinical outcomes in surgically treated patients with metastatic epidural spinal cord compression: results of the prospective multicenter AO spine study. J Clin Oncol 2016;34:268–76.
[48] Friedman SM, Mendelson DA, Bingham KW, Kates SL. Impact of a comanaged Geriatric Fracture Center on short-term hip fracture outcomes. Arch Intern Med 2009;169:1712–7.
[49] Goldhahn J, Suhm N, Goldhahn S, Blauth M, Hanson B. Influence of osteoporosis on fracture fixation–a systematic literature review. Osteoporosis Int 2008;19:761–72.
[50] Kammerlander C, Roth T, Friedman SM, Suhm N, Luger TJ, Kammerlander-Knauer U, et al. Ortho-geriatric service–a literature review comparing different models. Osteoporosis Int 2010;21:S637–46.
[51] Konrad G, Bayer J, Hepp P, Voigt C, Oestern H, Kaab M, et al. Open reduction and internal fixation of proximal humeral fractures with use of the locking proximal humerus plate. Surgical technique. J Bone Joint Surg Am 2010;92 (Suppl 1 Pt 1):85–95.
[52] Perren SM. The concept of biological plating using the limited contact-dynamic compression plate (LC-DCP). Scientific background, design and application. Injury 1991;22(Suppl 1):1–41.
[53] Perren SM. Evolution of the internal fixation of long bone fractures. The scientific basis of biological internal fixation: choosing a new balance between stability and biology. J Bone Joint Surg Br 2002;84:1093–110.
[54] Ruedi T. Fractures of the lower end of the tibia into the ankle joint: results 9 years after open reduction and internal fixation. Injury 1973;5:130–4.
[55] Ruedi T, Matter P, Allgower M. [Intra-articular fractures of the distal tibial end]. Helv Chir Acta 1968;35:556–82.
[56] Rüedi TP, Allgower M. The operative treatment of intra-articular fractures of the lower end of the tibia. Clin Orthop Relat Res 1979;105–10.
[57] Ruedi TP, Luscher JN. Results after internal fixation of comminuted fractures of the femoral shaft with DC plates. Clin Orthop Relat Res 1979;74–6.
[58] Jeannet J-P. AO Institutes: Res earch, CDID, 'Trauma University,' and a Publishing House (Chapter 45). Leading a Surgical Revolution The AO Foundation – Social Entrepreneurs in the Treatment of Bone Trauma. Springer Nature Switzerland: Cham; 2019. p. 335–50.
[59] Cutler DM, Long G, Berndt ER, Royer J, Fournier AA, Sasser A, et al. The value of antihypertensive drugs: a perspective on medical innovation. Health Aff (Project Hope) 2007;26:97–110.
[60] Schneider R. 10 Jahre AO: AO - Dokumentationszentrale Bern, 1969.
[61] Schneider R. 25 Jahre AO-Schweiz - Arbeitsgemeinschaft für Osteosynthesefrage 1958-1983: Arbeitsgemeinschaft fuer Osteosynthesefragen. 1983.
[62] Schlich T. Surgery, science and industry – A revolution in fracture care, 1950s-1990s. New York: Palgrave MacMillan; 2002.